National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

（NCCN腫瘍学臨床診療ガイドライン）

乳　癌

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NCCN.org

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NCCN Guidelines Version 1.2018
乳癌

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NCCNガイドライン委員会に関する情報開示

NCCN Guidelines Version 1.2018
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臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

NCCN加盟施設における臨床試験のオンライン検索はこちらから：nccn.org/clinical_trials/clinicians.html.

NCCNのエビデンスとコンセンサスによるカテゴリー：特に指定のない限り、すべての推奨はカテゴリー2Aである。

NCCNのエビデンスとコンセンサスによるカテゴリー. を参照。

NCCNの望ましさのカテゴリー：いずれの推奨も適切と考えられる。

NCCNの望ましさのカテゴリーを参照。

乳癌ガイドライン2017年第4版から2018年第1版への更新内容は以下の通りである：

DCIS-1
- 脚注「h」が変更された：乳房全切除術または再切除術の時点で浸潤性と判明した患者は、リンパ節病期診断を含めて*臨床*病期I期またはII期（ST-1を参照）として管理する。

BINV-1
- 最下部の分岐「術前薬物療法を考慮している場合」に*T0-3, N2, M0*、*T4, N0-2, M0*および*Any T, N3, M0*が追加された。

BINV-5
- 脚注「ee」が変更された：~~I期が~~*T1, N0, M0*に置き換えられた。
- 脚注「ff」が変更された：再発リスクが高い~~（II～III期）~~と考えられるHR陽性*HER2陽性*例には、トラスツズマブを含む術後療法に続いてneratinibによる更なる術後療法を考慮する。ペルツズマブの投与を受けた患者におけるneratinibによる追加治療の利益や毒性については不明である。（BINV-13および15も同様）

BINV-10
- 脚注「kk」が変更された：~~（IIB期およびIIIA期）が~~（*T2, N0, M0*、*T3, N0, M0*、*T3, N1, M0*）に置き換えられた。

BINV-17
- 精査、以下が追加された：単剤療法に適格なHER2陰性例には、生殖細胞系BRCA 1/2変異の検査を強く考慮

BINV-20
- 過去1年以内の内分泌療法による治療歴なし、閉経後：
  - ~~パルボシクリブ＋アロマターゼ阻害薬（カテゴリー1）またはRibociclib＋アロマターゼ阻害薬（カテゴリー1）が~~CDK4/6阻害薬＋アロマターゼ阻害薬（カテゴリー1）に置き換えられた。
- 過去1年以内の内分泌療法による治療歴なし、閉経前：
  - ~~またはmTOR阻害薬が~~削除された。

BINV-21、BINV-24～BINV-26.
- 脚注「iii」が新たに追加された：全身状態（PS）が不良の患者では、化学療法を追加することで潜在的な副作用が臨床的利益を上回る可能性がある。

BINV-D
- 本ページの見出しと最初のノードに*T0, N1, M0*が追加された。

BINV-K
- 術前/術後療法のレジメン
  - レジメンが「望ましいレジメン」、「特定の状況で有用」および「その他の推奨レジメン」に分類された。
  - 脚注「7」が新たに追加された：パクリタキセルとその後のDose-dense（投与間隔短縮）ACへの投与順序の変更が受け入れられる。
  - 脚注「9」が変更された： 低リスクかつ*T1, N0, M0*~~I期~~のHER2陽性乳癌患者（特に、併存疾患のために他の標準的な術後療法レジメンに不適格とされた患者）には、パクリタキセル＋トラスツズマブを考慮してもよい。
- HER2陰性、以下のレジメンが「特定の状況で有用」から「その他の推奨レジメン」に移動された。
  - ACに続いてドセタキセルを3週間毎
  - EC（エピルビシン/シクロホスファミド）
  - TAC（ドセタキセル/ドキソルビシン/シクロホスファミド）
- HER2陽性、パクリタキセル＋トラスツズマブが「その他の推奨レジメン」から「望ましいレジメン」に移動された。
- HER2陽性、ドセタキセル＋シクロホスファミド＋トラスツズマブが「その他の推奨レジメン」から「特定の状況で有用」に移動された。

BINV-N
- ERおよび/またはPR陽性再発/IV期（M1）に対する全身療法、本ページから閉経前女性に対する選択肢が削除された。この情報は、アルゴリズムのBINV-20に掲載されている。
- HER2陰性かつ閉経前：
  - 以下が追加された：望ましいレジメンの選択肢としてabemaciclib＋アロマターゼ阻害薬（カテゴリー1）。
  - 脚注「3」が変更され、「パルボシクリブまたはribociclib」が「CDK4/6阻害薬」に置き換えられた。
  - 以下が追加された：望ましいレジメンの選択肢としてribociclib＋タモキシフェン（カテゴリー1）。
    - ◊ 脚注「7」が新たに追加された：閉経前のホルモン受容体陽性HER2陰性転移乳癌患者の一次治療選択肢として卵巣抑制または卵巣切除を考慮してもよい。

続く

乳癌ガイドライン2017年第4版から2018年第1版への更新内容は以下の通りである：

- 以下が「特定の状況で有用」に移動された。
  - ◊ 酢酸メゲストロール
  - ◊ フルオキシメステロン
  - ◊ エチニルエストラジオール
  - ◊ Abemaciclib

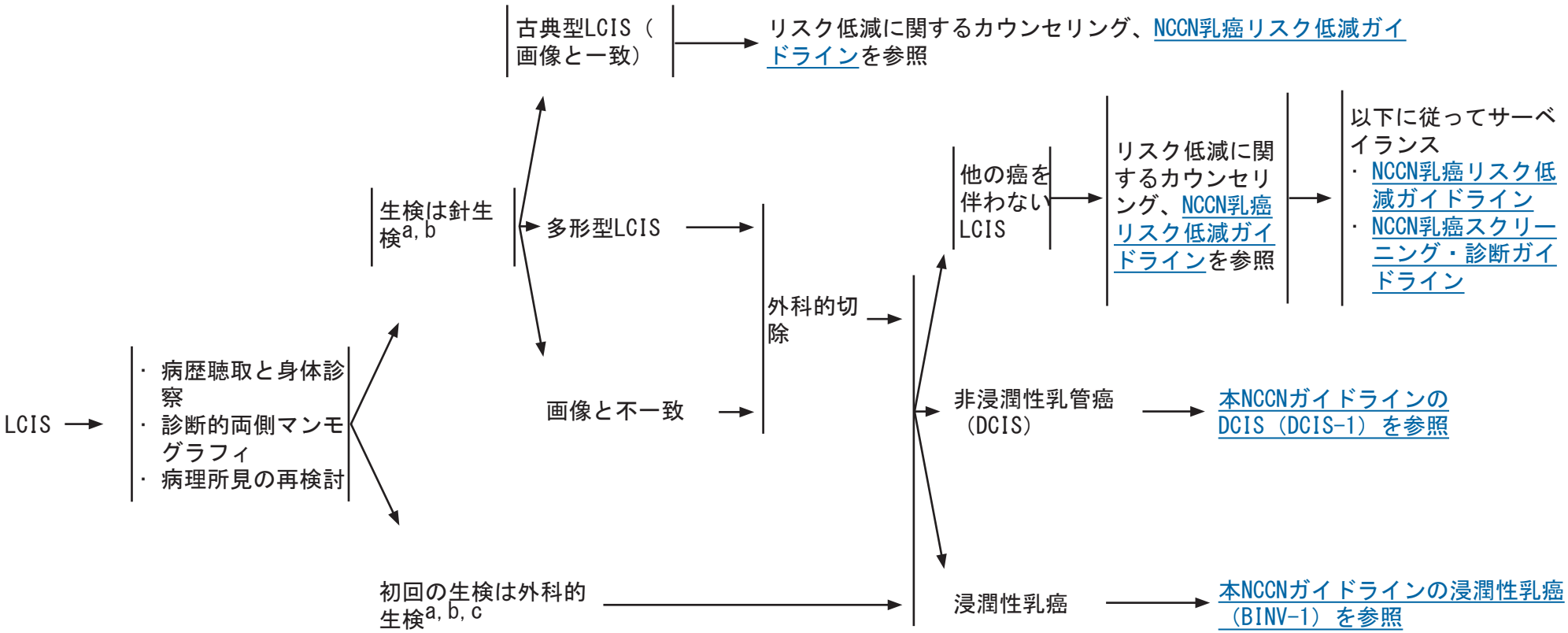
BINV-O

・ 再発/IV期（M1）に対する化学療法レジメン
- レジメンが「望ましいレジメン」、「特定の状況で有用」および「その他の推奨レジメン」に分類された。
- ペグ化リポソーム封入ドキソルビシンから~~ペグ化が~~削除された。
- オラパリブが変更されて以下が追加された： *（HER2陰性乳癌で生殖細胞系BRCA1/2変異を有する患者に対する選択肢）*
- 以下の併用レジメンが削除された：
  - ◊ CAF/FAC（シクロホスファミド/ドキソルビシン/フルオロウラシル）
  - ◊ FEC（フルオロウラシル/エピルビシン/シクロホスファミド）
- 下位見出し~~のトラスツズマブ曝露歴のあるHER2陽性乳癌に対する薬剤~~が削除された。
- 脚注「2」が変更された：~~併用療法が単剤の連続使用より優れていることを示す説得性のあるエビデンスは存在しない。~~単剤の連続使用が望ましいが、腫瘍量が多く、急速進行性で生命を脅かす内臓転移のある選択された患者では、併用化学療法が使用できる。

病期分類

・ 病期分類が更新され、出典がAJCC Cancer Staging Manual第8版（2017年）に変更された。

診断　精査　リスク低減　サーベイランス



a 別の増殖性変化（異型乳管過形成または異形小葉過形成）の有無を問わず、LCISが初回（針または外科的）生検または最終切除標本に認められる。
b 一部のLCISの亜型（多形型LCIS）は、DCISとほぼ同じ生物学的挙動を示すことがある。臨床医は、多形型LCISに対して断端陰性の完全切除を考えても差し支えないが、それにより臨床的有益性が証明されていない乳房全切除術の実施率が高くなる可能性がある。この場合に放射線療法を行うことを支持するデータはない。
c 針生検で終末乳管小葉単位4ヵ所を超えて広がる多病巣性/広汎性LCISを認めた場合、外科的切除標本で浸潤癌と診断されるリスクが高まる場合がある。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

診断 | 精査 | 一次治療

DCIS
Tis, N0, M0

→ 精査
- 病歴聴取と身体診察
- 診断的両側マンモグラフィ
- 病理所見の再検討[a]
- 腫瘍のエストロゲン受容体（ER）の発現状況の判定
- 遺伝性乳癌のリスクが高い場合は遺伝カウンセリング[b]
- 乳房MRI[c,d]（必要に応じて）

→ 一次治療

腋窩手術[f]を行わない乳房部分切除術[e]＋腫瘍床へのブースト照射を伴うまたは伴わない全乳房放射線照射（カテゴリー1）[g,h,i,j]
または
センチネルリンパ節生検[f,h]を伴うまた伴わない乳房全切除術＋乳房再建（任意）[k]
または
放射線療法を行わなず腋窩手術[f]を行わない乳房部分切除術[e,g,h,i,j]（カテゴリー2B）

→ 術後の治療（DCIS-2）を参照

a 当委員会は、すべての浸潤性および非浸潤性乳癌の病理報告についてCollege of American Pathologists Protocolを支持している。http://www.cap.org
b NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。
c 乳房MRI検査の原則（BINV-B）を参照のこと。
d MRIの使用により、断端陰性が得られる可能性が高まったり、乳房全切除への切替えが減る効果は示されていない。長期成績の改善を裏付けるデータはない。
e 乳房温存療法を希望する患者では、断端陰性を得るために再切除を行ってもよい。乳房部分切除術で十分な切除縁が得られない患者には乳房全切除術を施行すべきである。十分な切除縁の定義については、DCISおよび浸潤性乳癌に対する断端状態による推奨（BINV-F）を参照のこと。
f DCISとみられる患者で浸潤癌の所見が認められず、腋窩リンパ節転移が証明されていない場合には、完全な腋窩リンパ節郭清を行うべきではない。ただし、DCISとみられる患者のごく一部では、最終手術の時点で浸潤癌の存在が判明する場合がある。したがって、DCISとみられる患者で乳房全切除術による治療や、後日のセンチネルリンパ節生検を妨げるような解剖学的位置での切除が予定されている場合には、センチネルリンパ節生検の施行を強く考慮すべきである。
g 放射線療法の原則（BINV-I）を参照のこと。
h 乳房全切除術または再切除術の時点で浸潤性と判明した患者は、リンパ節病期診断を含めて臨床病期I期またはII期（ST-1を参照）として管理する。
i 放射線療法を要する乳房温存療法に関する特別な考慮点（BINV-G）を参照のこと。
j 乳房部分切除術とそれに続く全乳房放射線照射により非浸潤性乳管癌における再発率はおよそ50%低下する。再発例のおよそ半数は浸潤性乳癌、半数は非浸潤性乳管癌である。いくつかの因子が局所再発リスクを左右する：例えば、触知可能な腫瘤、腫瘍径が大きい、グレードが高い、切除断端近接または陽性、年齢50歳未満などである。再発リスクが「低い」と考える場合、一部の患者では切除手術のみの治療も許容される。3つの局所療法を比較したデータでは、患者の生存期間に差はみられていない。
k 術後乳房再建の原則（BINV-H）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

DCISの術後の治療

乳房温存手術後の同側乳房のリスク低減療法：
・ 次の患者には5年間の内分泌療法を考慮：
  ▸ 乳房温存手術（乳房部分切除術）と放射線療法[m]（カテゴリー1）による治療を受けた患者、特にER陽性のDCIS患者
  ▸ ER陰性DCISに対する内分泌療法の有益性は不明である
  ▸ 切除のみによる治療を受けた患者[l]
・ 内分泌療法：
  ▸ 閉経前患者にはタモキシフェン[m]
  ▸ 閉経後患者にはタモキシフェン[m]またはアロマターゼ阻害薬、60歳未満または血栓塞栓症の懸念がある患者ではアロマターゼ阻害薬の方がやや優れている

対側乳房のリスク低減療法：
・ リスク低減に関するカウンセリング
  NCCN乳癌リスク低減ガイドラインを参照

サーベイランス/フォローアップ

・ 5年間は6～12ヵ月毎、以後は1年毎の病歴聴取および身体診察
・ 12ヵ月毎のマンモグラフィ（乳房温存療法の6～12ヵ月後に最初のマンモグラフィ、カテゴリー2B）
・ 内分泌療法で治療する場合は、NCCN乳癌リスク低減ガイドラインに従ってモニタリング

[l] 現存するデータによると、乳房温存療法を受けた患者の同側乳癌の再発リスクとER陽性原発腫瘍に対して乳房全切除術または乳房温存手術による治療を受けた患者の対側乳癌の再発リスクは、内分泌療法によって低減されることが示唆される。生存に対する治療効果は実証されていないため、個別にリスクとベネフィットを考慮することが重要である（NCCN乳癌リスク低減ガイドラインも参照）。
[m] タモキシフェンの使用を検討している女性におけるCYP2D6の遺伝子型検査は推奨されない。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

臨床病期

精査

T1, N0, M0

T0, N1, M0[a]
T1, N1, M0[a]
T2, N0, M0

T2, N1, M0
T3, N0, M0

T3, N1, M0

T0-3, N2, M0
T4, N0-2, M0
Any T, N3, M0

- 病歴聴取と身体診察
- 診断的両側マンモグラフィ、必要に応じて超音波検査
- 病理所見の再検討[b]
- 腫瘍のエストロゲン/プロゲステロン受容体（ER/PR）およびHER2の発現状況を判定[c]
- 遺伝性乳癌のリスクが高い患者の場合は遺伝カウンセリング[d]
- 乳房MRI[e]（任意）、マンモグラフィで発見されない腫瘍に特に注意
- 閉経前であれば妊孕性の懸念に関するカウンセリング；妊娠可能なすべての女性で妊娠検査[f]
- 精神的苦痛の評価[g]

臨床病期がI期～IIB期の患者には、徴候または症状から必要と判断される場合に限り、以下の追加検査を考慮：[h]

- 血算
- 肝機能検査およびアルカリホスファターゼを含む生化学検査（comprehensive metabolic panel）
- 骨シンチグラフィ（限局性の骨痛またはアルカリホスファターゼ上昇がある場合）
- 腹部±骨盤の画像診断用造影CTまたは造影MRI（アルカリホスファターゼ上昇、肝機能検査値異常、腹部症状、腹部または骨盤の身体診察で異常が認められる場合）
- 胸部の画像診断用造影CT（肺症状がみられる場合）

臨床病期がIIIA期（T3, N1, M0）の場合、以下の検査を強く考慮：

- 血算
- 肝機能検査およびアルカリホスファターゼを含む生化学検査（comprehensive metabolic panel）
- 胸部の画像診断用造影CT
- 腹部±骨盤の画像診断用造影CTまたは造影MRI
- 骨シンチグラフィまたはSodium Fluoride PET/CT[i]（カテゴリー2B）
- FDG PET/CT[j,k]（任意）

→ 局所療法（BINV-2）を参照[l]

術前薬物療法を考慮している場合 → 手術可能例に対する術前薬物療法：精査（BINV-10）を参照
または
手術不能または局所進行例（非炎症性）に対する術前薬物療法：精査（BINV-14）を参照

[a] HER2陽性のN1腫瘍に術前薬物療法を考慮する場合、術前薬物療法の原則（BINV-L）および精査（BINV-10）を参照のこと。
[b] 当委員会は、すべての浸潤性および非浸潤性乳癌の病理報告についてCollege of American Pathologists Protocolを支持している。http://www.cap.org。
[c] HER2検査の原則（BINV-A）を参照のこと。
[d] NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。
[e] 乳房MRI検査の原則（BINV-B）を参照のこと。
[f] 妊孕性および避妊（BINV-C）を参照のこと。
[g] NCCN Guidelines for Distress Managementを参照のこと。
[h] 症状がみられない早期乳癌に対しては、ルーチンな全身の病期診断は適応とならない。
[i] FDG PET/CTを施行して、PETとCTの両要素から骨転移が明白に示された場合には、骨シンチグラフィまたはSodium Fluoride PET/CTは必要ないと考えられる。
[j] FDG PET/CTは診断目的のCTと同時に施行できる。臨床病期がI期、II期または手術可能なIII期の乳癌では、PETまたはPET/CTは適応とならない。FDG PET/CTは、標準的な病期診断検査では結果が曖昧であるか疑わしい状況で最も有用となる（特に局所進行例または転移例の場合）。
[k] FDG PET/CTは、標準的な病期診断検査に加えて用いる場合、局所進行乳癌において疑われていない領域リンパ節病変や遠隔転移を同定するのにも有用となりうる。
[l] 治療の特別な考慮事項については、NCCN Guidelines for Older Adult Oncologyを参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

T1-3, N0-1, M0期の局所療法[l]

外科的腋窩病期診断を伴う乳房部分切除術（カテゴリー1）[m,n,o]

- 4個以上の陽性腋窩リンパ節[r] → 腫瘍床（カテゴリー1）、鎖骨下領域、鎖骨上領域、内胸リンパ節、およびリスクのある腋窩切除床のあらゆる部分（カテゴリー1）に対するブースト照射[s]を併用するまたは併用しない全乳房照射。化学療法の適応がある場合は、放射線療法は化学療法後に施行するのが一般的である。
- 1～3個の陽性腋窩リンパ節 → 腫瘍床へのブースト照射[r]を併用するまたは併用しない全乳房照射（カテゴリー1）。鎖骨下領域、鎖骨上領域、内胸リンパ節、およびリスクのある全腋窩領域に対する放射線療法を強く考慮する。化学療法の適応がある場合は、放射線療法は化学療法後に施行するのが一般的である。
- 腋窩リンパ節転移陰性 → 腫瘍床へのブースト照射[s]を併用するまたは併用しない全乳房照射、および中央／内側の腫瘍または2cmを超える腫瘍で他の高リスクの特徴（若年または広範なリンパ管侵襲［LVI］）を有する患者では領域リンパ節照射を考慮する。
または
選択された低リスク患者には加速乳房部分照射法（accelerated partial breast irradiation：APBI）を考慮する[s,t]。
化学療法の適応がある場合は、放射線療法は化学療法後に施行するのが一般的である[u]。

または

外科的腋窩病期診断を伴う乳房全切除術[m,n,p]（カテゴリー1）±再建術[q] → 局所療法（BINV-3）を参照

または

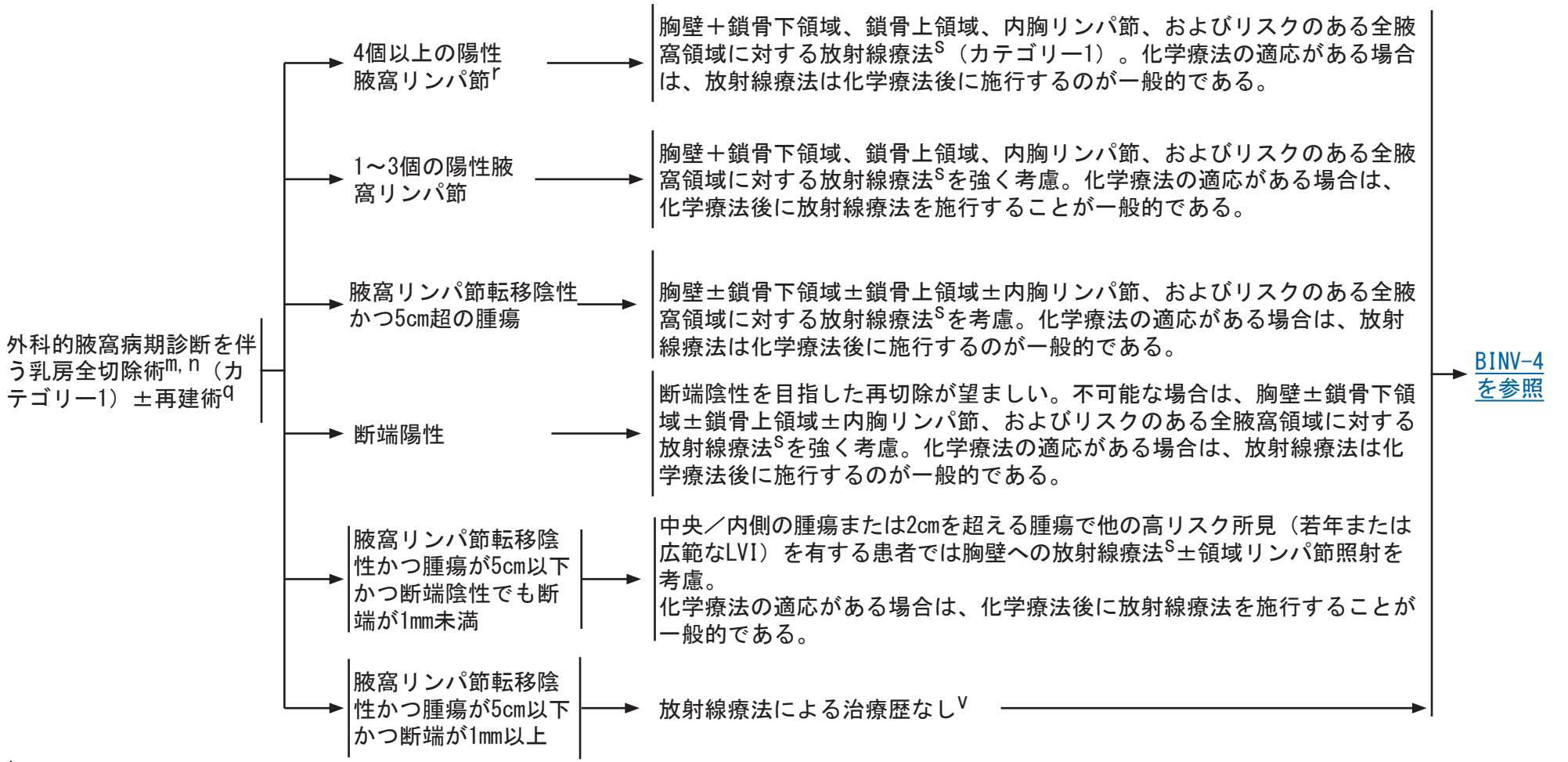
T2またはT3で、大きさ以外の乳房温存療法の基準を満たしている場合[o] → 術前薬物療法（BINV-10）のガイドラインを考慮

BINV-4を参照

[l] 治療の特別な考慮事項については、NCCN Guidelines for Older Adult Oncologyを参照のこと。
[m] 外科的腋窩病期診断（BINV-D）を参照のこと。
[n] 腋窩リンパ節病期診断（BINV-E）とDCISおよび浸潤性乳癌に対する断端状態による推奨（BINV-F）を参照のこと。
[o] 放射線療法を要する乳房温存療法に関する特別な考慮点（BINV-G）を参照のこと。
[p] NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインおよびNCCN乳癌リスク低減ガイドラインに概説する場合を除き、既知片側乳癌の対側乳房に対する予防的乳房全切除術は推奨されない。これを考慮する場合、片側乳癌患者に対する予防的対側乳房全切除によって得られるわずかな利益と同側乳癌再発のリスク、両側乳房全切除による心理的および社会的問題ならびに対側乳房全切除によるリスクをはかりにかけなければならない。乳房温存療法が行われた乳房の対側乳房に対して予防的乳房全切除を行うことには、極めて強く反対する。
[q] 術後乳房再建の原則（BINV-H）を参照のこと。
[r] 病期診断のため、胸部/腹部±骨盤の画像診断用造影CT、骨シンチグラフィ、および任意のFDG PET/CTを含む全身の画像検査を考慮する(BINV-1を参照)。
[s] 放射線療法の原則（BINV-I）を参照のこと。
[t] PBIは化学療法の前に施行してもよい。
[u] 乳房に対する放射線療法は、70歳以上でエストロゲン受容体陽性かつ臨床的リンパ節転移陰性のT1腫瘍に対して術後内分泌療法を受ける患者では省略可能である（カテゴリー1）。

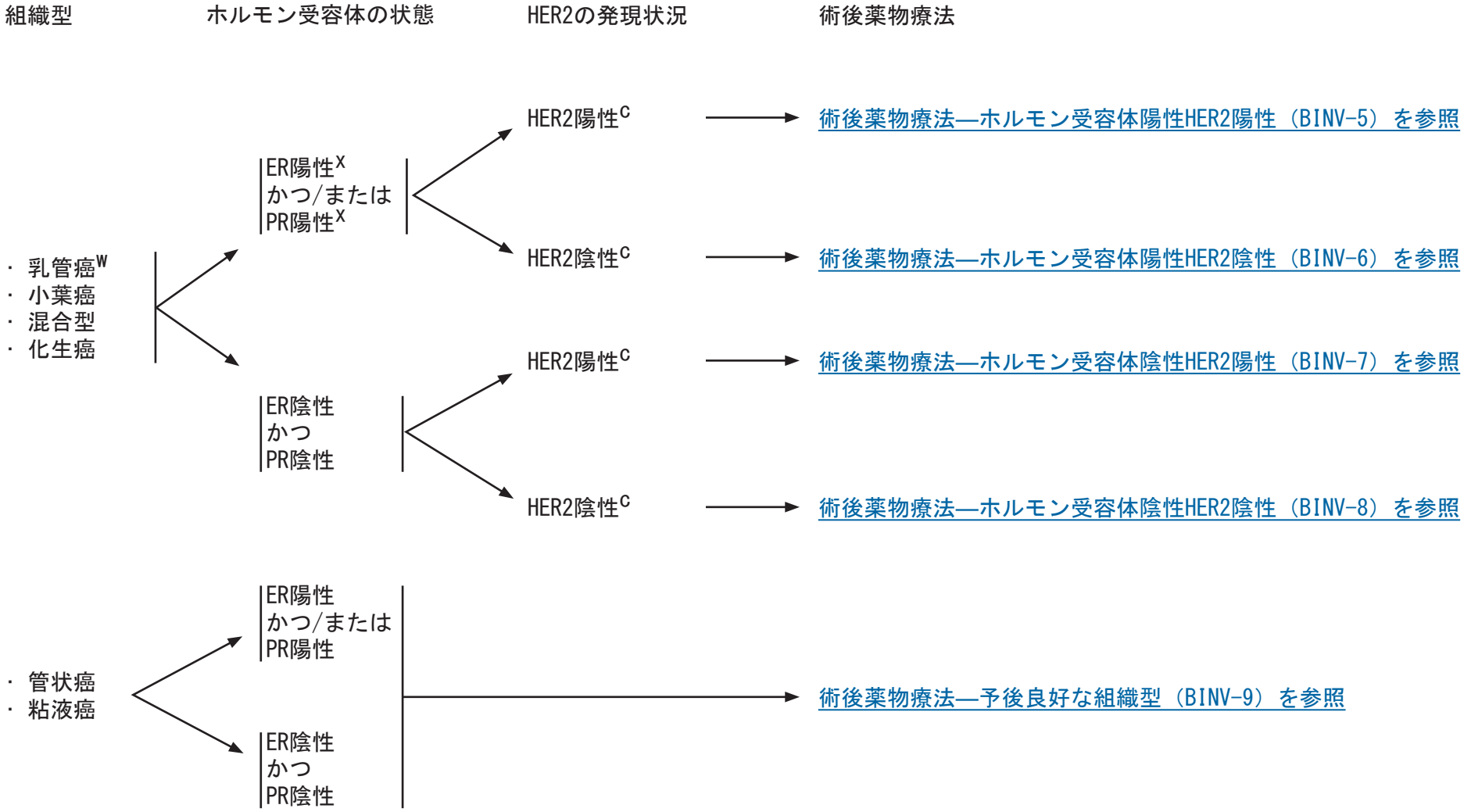
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

T1-3, N0-1, M0期の局所療法[l]



[l] 治療の特別な考慮事項については、NCCN Guidelines for Older Adult Oncologyを参照のこと。
[m] 外科的腋窩病期診断（BINV-D）を参照のこと。
[n] 腋窩リンパ節病期診断（BINV-E）とDCISおよび浸潤性乳癌に対する断端状態による推奨（BINV-F）を参照のこと。
[q] 術後乳房再建の原則（BINV-H）を参照のこと。
[r] 病期診断のため、胸部/腹部±骨盤の画像診断用造影CT、骨シンチグラフィ、および任意のFDG PET/CTを含む画像検査を考慮する（BINV-1を参照）。
[s] 放射線療法の原則（BINV-I）を参照のこと。
[v] 中央／内側の腫瘍または2cmを超える腫瘍で若年または広範なLVIを有するなど、複数の高リスク再発因子を有する患者には乳房全切除術後の放射線療法を考慮してもよい。

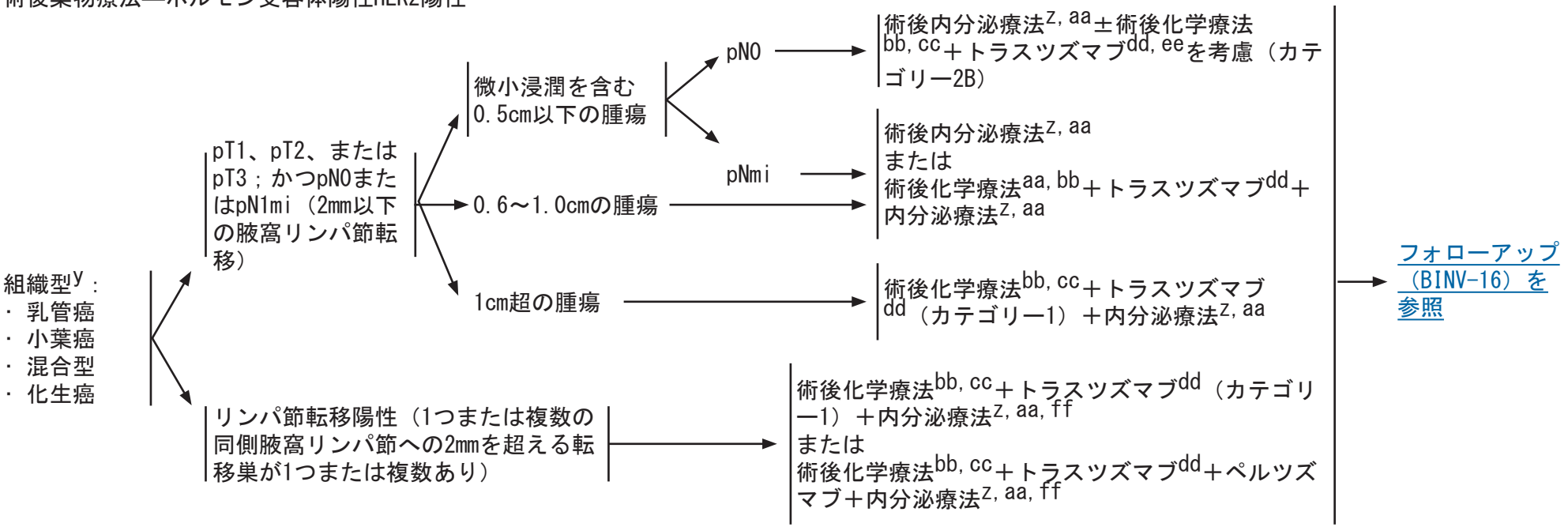
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[C] HER2検査の原則（BINV-A）を参照のこと。
[W] 髄様癌および浸潤性微小乳頭癌を含む。
[X] 乳癌におけるERおよびPRの発現は、低い（1～10%）ものから高いものまでに及ぶ可能性がある。ER/PRの発現が低い腫瘍の生物学的ふるまいは、ER/PR陰性腫瘍と極めて類似していることがあり、このことは術後療法の意思決定で考慮しておくべきである。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術後薬物療法—ホルモン受容体陽性HER2陽性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。

[y] 小葉癌と乳管癌の混合型は、乳管癌成分でグレードを判定し、そのグレードに基づいて治療すべきである。化生癌については、組織学的なグレード判定の予後予測上の価値は不明である。ただし、特定の組織型の化生癌が認められ、腫瘍に占める割合が10%を超える場合には、その組織型は独立した予後因子となる。

[z] 術後療法を受けている閉経後（自然または人工）の患者では、ビスホスフォネート系薬剤による術後療法を考慮する。

[aa] ホルモン受容体陽性乳癌の閉経前女性における卵巣摘出術または放射線療法による卵巣機能の抑制の効果の大きさはCMF単独で達成されるものと同程度であることが、エビデンスによって裏付けられている。術後内分泌療法（BINV-J）を参照のこと。

[bb] 術後療法としての化学療法と内分泌療法は、化学療法に続いて内分泌療法という順序で逐次的に施行すべきである。現時点で得られているデータによると、放射線療法と内分泌療法の逐次または同時併用は許容できることが示唆される。術後内分泌療法（BINV-J）および術前/術後療法のレジメン（BINV-K）を参照のこと。

[cc] 70歳以上の患者に対して化学療法の推奨を示すためのデータは限られている。NCCN Clinical Practice Guidelines for Older Adult Oncologyを参照のこと。

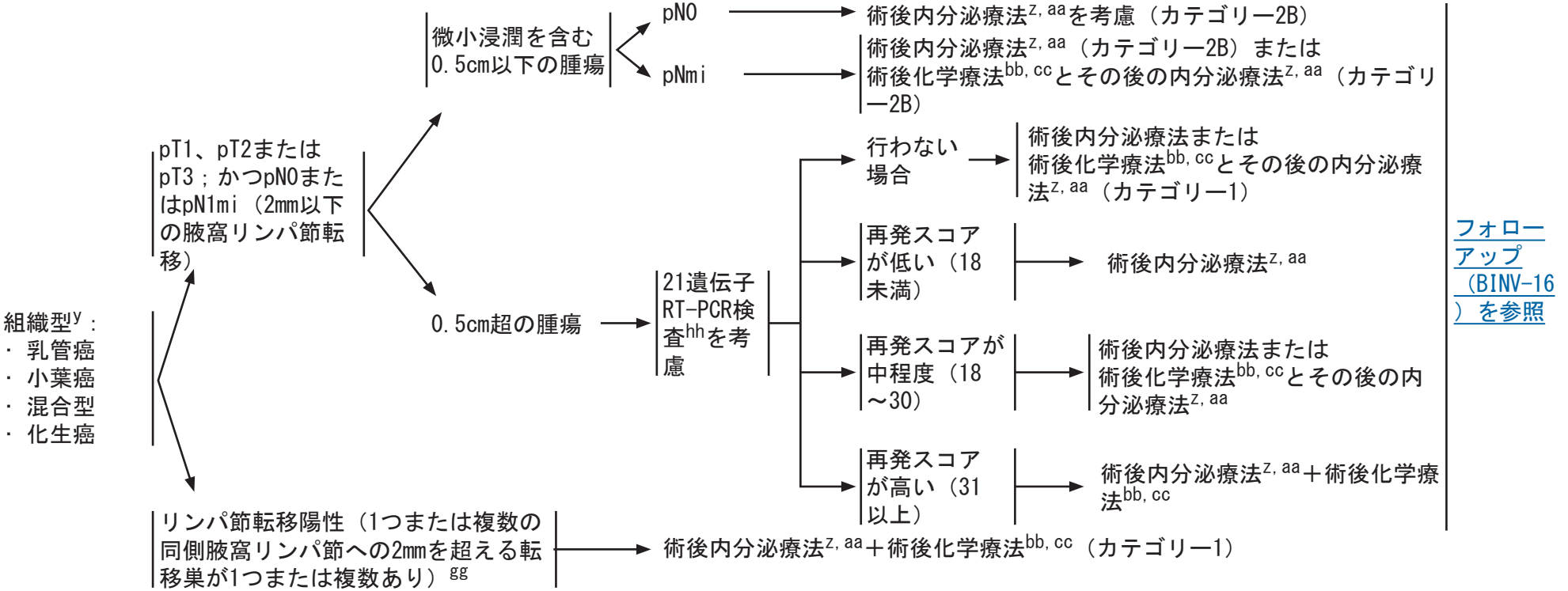
[dd] リンパ節転移陰性のT1aおよびT1b例の予後は、たとえHER2の増幅または過剰発現がみられる場合でも、不明確である。このような患者は、実施されたランダム化試験で検討されなかった乳癌患者集団である。この患者集団にトラスツズマブ治療を使用するか否かは、トラスツズマブの既知の毒性（心毒性など）とトラスツズマブの投与により得られると考えられる不確実ではあるが絶対的な利益を比較して決断しなければならない。

[ee] T1, N0, M0のHER2陽性乳癌（特に原発癌がER陰性の場合）には、パクリタキセル週1回による術後化学療法＋トラスツズマブ（Tolaney et al. NEJM 2015）を考慮することができる。ER陽性癌で腫瘍の大きさがT1mic（1mm未満）の境界にある患者において、推定再発リスクが5%未満で、内分泌療法が依然として全身療法に対する有効な選択肢である場合は、HER2に基づく全身化学療法の絶対的利益はわずかである可能性が高い。

[ff] 再発リスクが高いと考えられるHR陽性HER2陽性例には、トラスツズマブを含む術後療法に続いてneratinibによる更なる術後療法を考慮する。ペルツズマブの投与を受けた患者におけるneratinibによる追加治療の利益や毒性については不明である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術後薬物療法—ホルモン受容体陽性HER2陰性[c]



c HER2検査の原則（BINV-A）を参照のこと。

y 小葉癌と乳管癌の混合型は、乳管癌成分でグレードを判定し、そのグレードに基づいて治療すべきである。化生癌については、組織学的なグレード判定の予後予測上の価値は不明である。ただし、特定の組織型の化生癌が認められ、腫瘍に占める割合が10%を超える場合には、その組織型は独立した予後因子となる。

z 術後療法を受けている閉経後（自然または人工）の患者では、ビスホスフォネート系薬剤による術後療法を考慮する。

aa ホルモン受容体陽性乳癌の閉経前女性における卵巣摘出術または放射線療法による卵巣機能の抑制の効果の大きさはCMF単独で達成されるものと同程度であることが、エビデンスによって裏付けられている。術後内分泌療法（BINV-J）を参照のこと。

bb 術後療法としての化学療法と内分泌療法は、化学療法に続いて内分泌療法という順序で逐次的に施行すべきである。現時点で得られているデータによると、放射線療法と内分泌療法の逐次または同時併用は許容できることが示唆される。術後内分泌療法（BINV-J）および術前/術後療法のレジメン（BINV-K）を参照のこと。

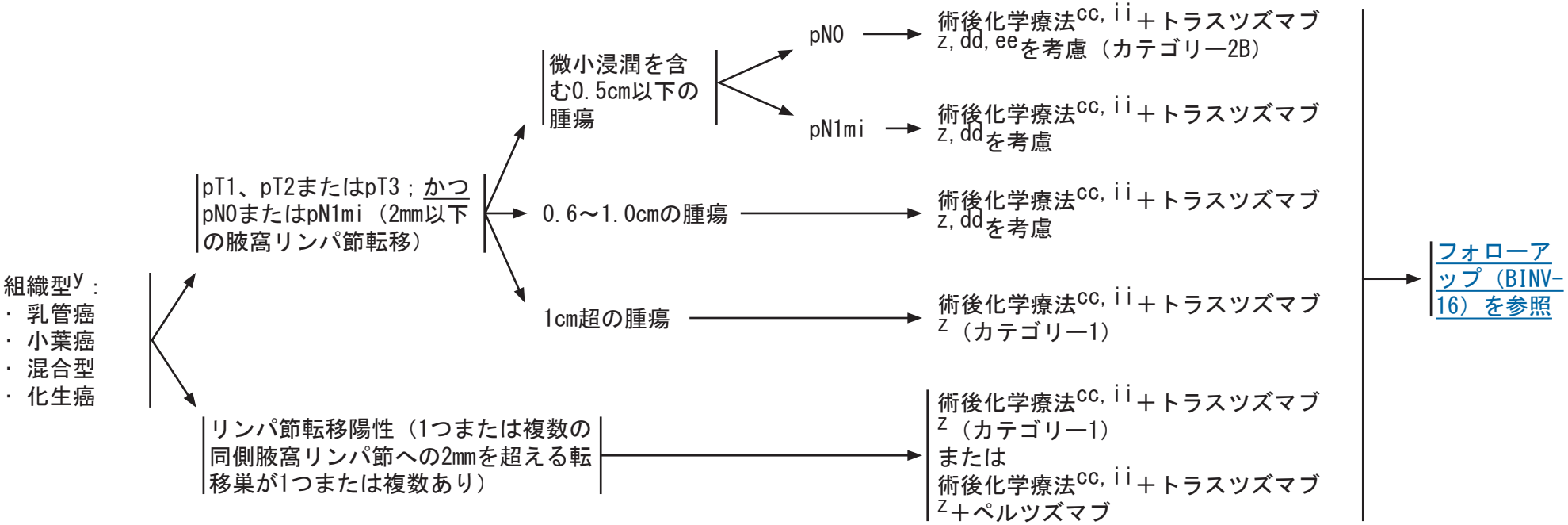
cc 70歳以上の患者に対して化学療法の推奨を示すためのデータは限られている。NCCN Clinical Practice Guidelines for Older Adult Oncologyを参照のこと。

gg 同側腋窩リンパ節に1～3個の転移を認める選択された患者では、標準的なホルモン療法に化学療法を追加する指針とするために、21遺伝子RT-PCR検査の再発スコアを考慮することができる。前向きのランダム化試験を後ろ向きに解析した結果によると、この検査にはこのような患者群でもリンパ節転移陰性と同様の予測能があることが示唆される。

hh 他の診断目的の多遺伝子検査は、再発リスク評価を補助する目的で考慮してもよいが、化学療法への反応を予測するという用途では妥当性が確認されていない。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術後薬物療法—ホルモン受容体陰性HER2陽性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。

[y] 小葉癌と乳管癌の混合型は、乳管癌成分でグレードを判定し、そのグレードに基づいて治療すべきである。化生癌については、組織学的なグレード判定の予後予測上の価値は不明である。ただし、特定の組織型の化生癌が認められ、腫瘍に占める割合が10%を超える場合には、その組織型は独立した予後因子となる。

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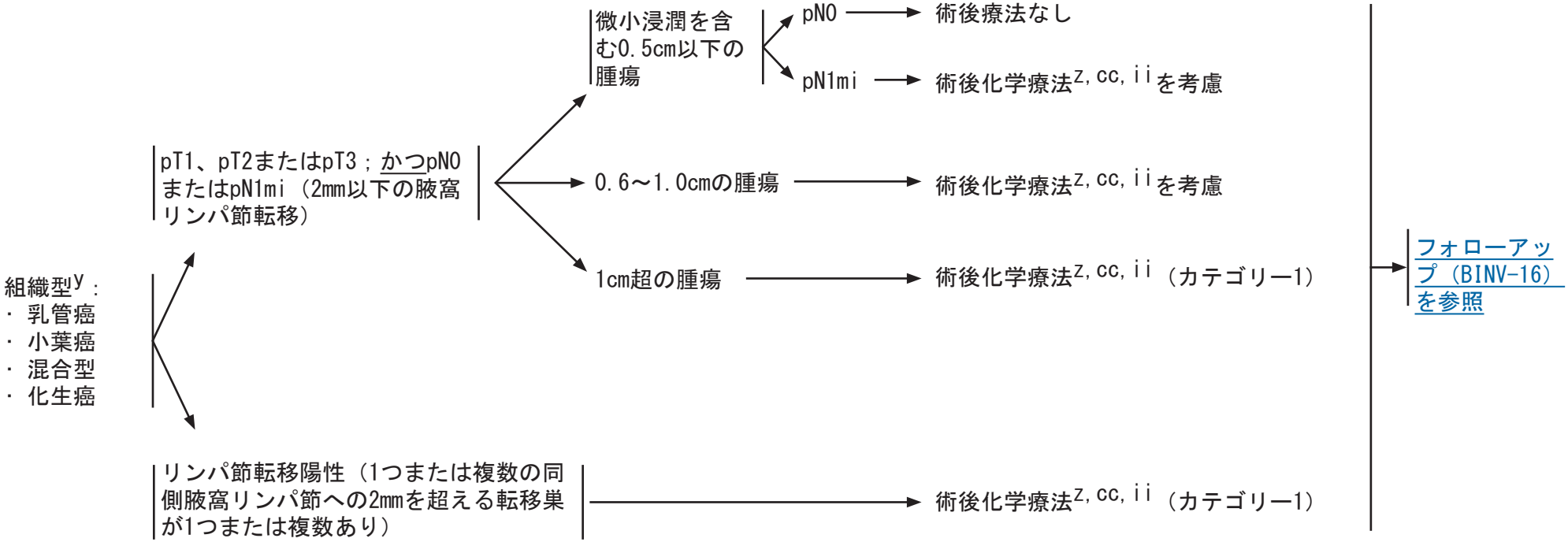
[ee] T1, N0, M0のHER2陽性乳癌（特に原発癌がER陰性の場合）には、術後化学療法＋パクリタキセルを週1回＋トラスツズマブ（Tolaney et al. NEJM 2015）を考慮することができる。ER陽性癌で腫瘍の大きさがT1mic（1mm未満）の境界にある患者において、推定再発リスクが5%未満で、内分泌療法が依然として全身療法に対する有効な選択肢である場合は、HER2に基づく全身化学療法の絶対的利益はわずかである可能性が高い。

[ii] 術前/術後療法のレジメン（BINV-K）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

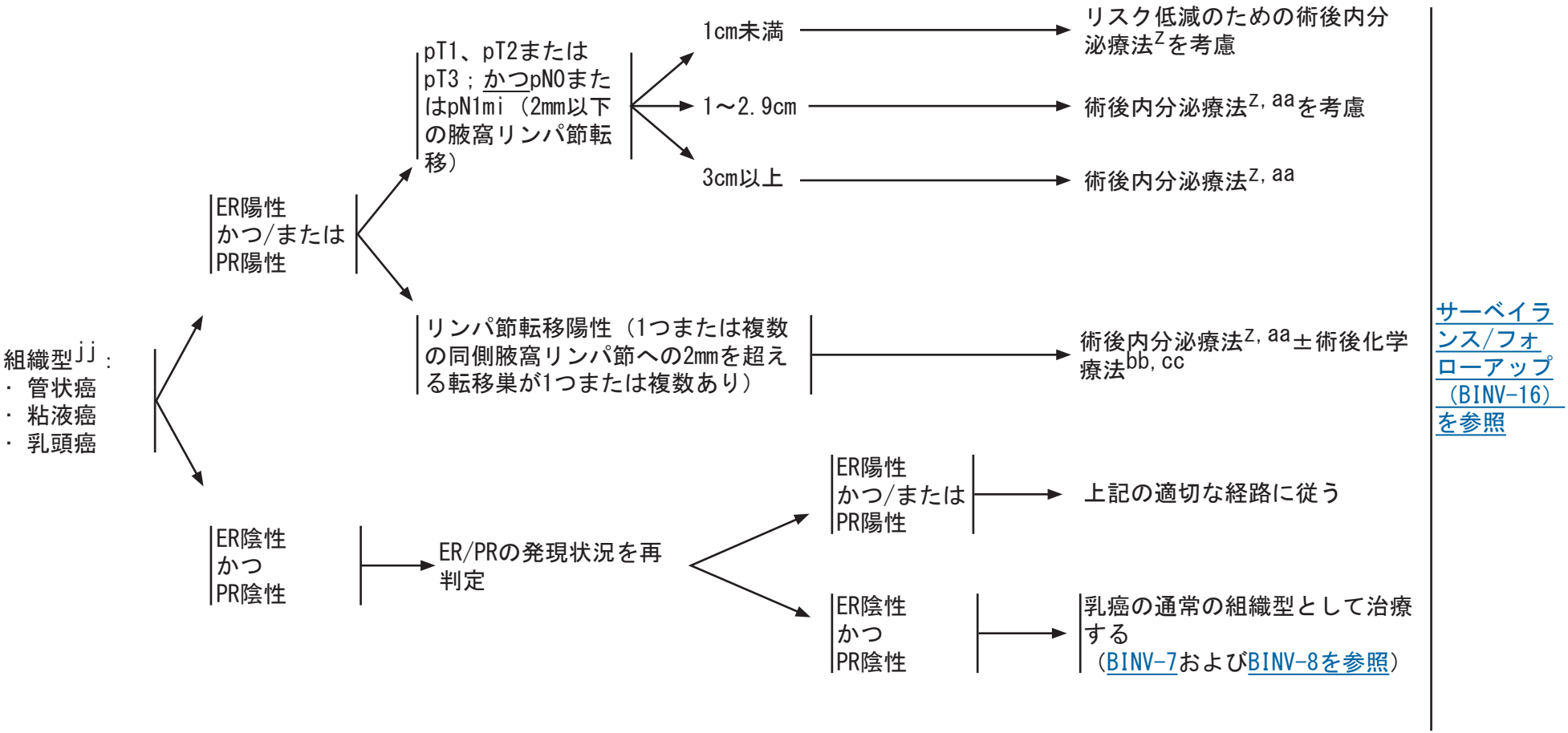
術後薬物療法—ホルモン受容体陰性HER2陰性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。
[y] 小葉癌と乳管癌の混合型は、乳管癌成分でグレードを判定し、そのグレードに基づいて治療すべきである。化生癌については、組織学的なグレード判定の予後予測上の価値は不明である。ただし、特定の組織型の化生癌が認められ、腫瘍に占める割合が10%を超える場合には、その組織型は独立した予後因子となる。
[z] 術後療法を受けている閉経後（自然または人工）の患者では、ビスホスフォネート系薬剤による術後療法を考慮する。
[cc] 70歳以上の患者に対して化学療法の推奨を示すためのデータは限られている。NCCN Clinical Practice Guidelines for Older Adult Oncologyを参照のこと。
[ii] 術前/術後療法のレジメン（BINV-K）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術後薬物療法—予後良好な組織型



z 術後療法を受けている閉経後（自然または人工）の患者では、ビスホスフォネート系薬剤による術後療法を考慮する。

aa ホルモン受容体陽性乳癌の閉経前女性における卵巣摘出術または放射線療法による卵巣機能の抑制の効果の大きさはCMF単独で達成されるものと同程度であることが、エビデンスによって裏付けられている。術後内分泌療法（BINV-J）を参照のこと。

bb 術後療法としての化学療法と内分泌療法は、化学療法に続いて内分泌療法という順序で逐次的に施行すべきである。現時点で得られているデータによると、放射線療法と内分泌療法の逐次または同時併用は許容できることが示唆される。術後内分泌療法（BINV-J）および術前/術後療法のレジメン（BINV-K）を参照のこと。

cc 70歳以上の患者に対して化学療法の推奨を示すためのデータは限られている。NCCN Clinical Practice Guidelines for Older Adult Oncologyを参照のこと。

jj 粘液癌や管状癌など、乳癌のまれな組織型の90%以上が含まれる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

手術可能例に対する術前薬物療法:精査
臨床病期

T2, N0, M0
T2, N1, M0
T3, N0, M0
T3, N1, M0

かつ

腫瘍の大きさ以外は乳房温存手術の基準を満たす[kk]

または

リンパ節転移陽性であるが、術前薬物療法によりリンパ節転移陰性になる可能性が高い

→

- 病歴聴取と身体診察
- 診断的両側マンモグラフィ、必要に応じて超音波検査
- 病理所見の再検討[b]
- 触診による腋窩リンパ節診断；必要に応じて超音波検査または他の画像検査、および疑わしいリンパ節の経皮的生検
- 腫瘍のER/PRおよびHER2の発現状況を判定[c]
- 遺伝性乳癌のリスクが高い患者の場合は遺伝カウンセリング[d]
- 乳房MRI[e]（任意）、マンモグラフィで発見されない腫瘍に特に注意
- 閉経前であれば妊孕性の懸念に関するカウンセリング；妊娠可能なすべての女性で妊娠検査[f]
- 精神的苦痛の評価[g]

以下の追加検査を考慮[h]：

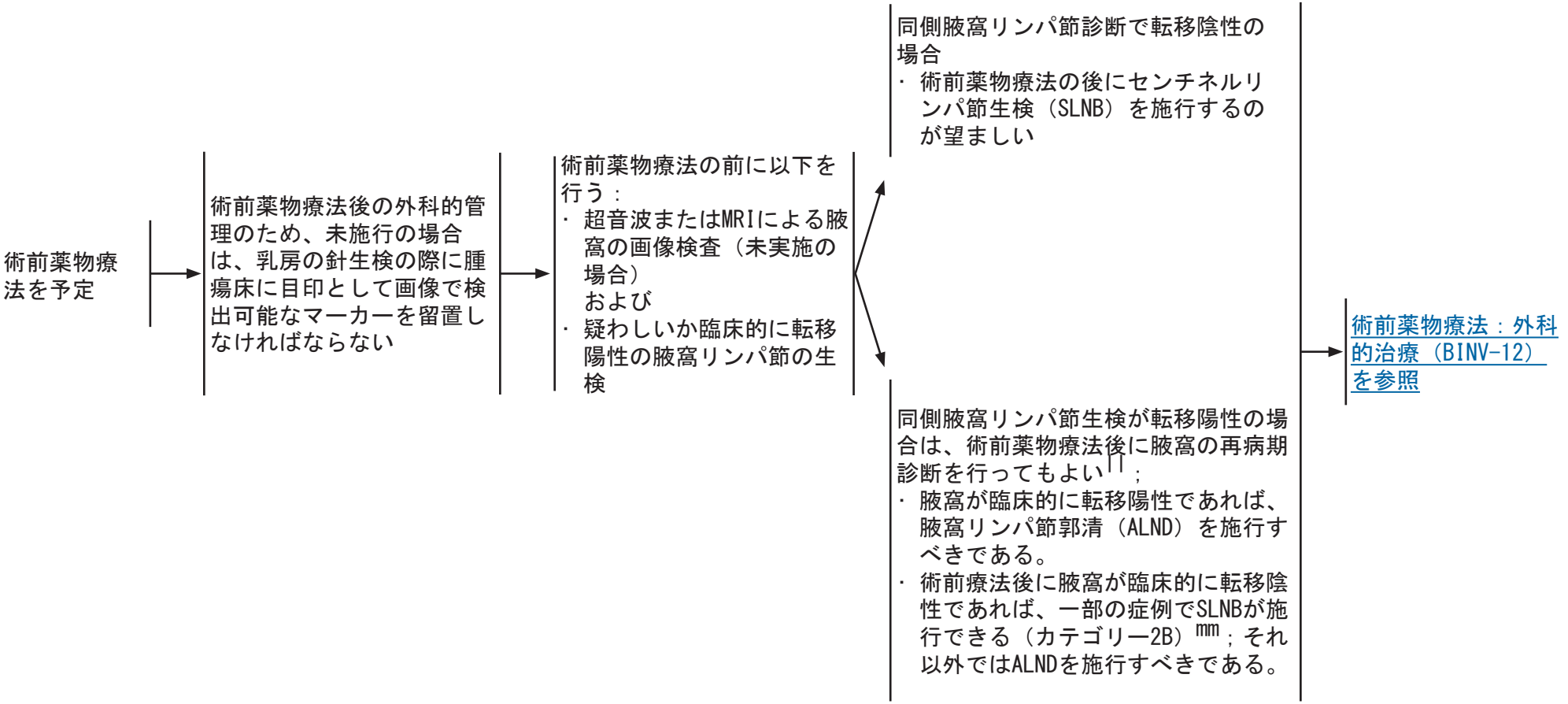
- 血算
- 肝機能検査およびアルカリホスファターゼを含む生化学検査（comprehensive metabolic panel）
- 胸部の画像診断用造影CT
- 腹部±骨盤の画像診断用造影CTまたは造影MRI
- 骨シンチグラフィまたはSodium Fluoride PET/CT[i]（カテゴリー2B）
- FDG PET/CT[j,k]（任意）

→ 術前薬物療法：乳房および腋窩リンパ節診断（BINV-11）を参照

[b] 当委員会は、すべての浸潤性および非浸潤性乳癌の病理報告についてCollege of American Pathologists Protocolを支持している。http://www.cap.org。
[c] HER2検査の原則（BINV-A）を参照のこと。
[d] NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。
[e] 乳房MRI検査の原則（BINV-B）を参照のこと。
[f] 妊孕性および避妊（BINV-C）を参照のこと。
[g] NCCN Guidelines for Distress Managementを参照のこと。
[h] 症状がみられない早期乳癌に対しては、ルーチンな全身の病期診断は適応とならない。
[i] FDG PET/CTを施行して、PETとCTの両要素から骨転移が明白に示された場合には、骨シンチグラフィまたはSodium Fluoride PET/CTは必要ないと考えられる。
[j] FDG PET/CTは診断目的のCTと同時に施行できる。臨床病期がI期、II期または手術可能なIII期の乳癌では、PETまたはPET/CTは適応とならない。FDG PET/CTは、標準的な病期診断検査では結果が曖昧であるか疑わしい状況で最も有用となる（特に局所進行例または転移例の場合）。
[k] FDG PET/CTは、標準的な病期診断検査に加えて用いる場合、局所進行乳癌において疑われていない領域リンパ節病変や遠隔転移を同定するのにも有用となりうる。
[kk] 乳房温存手術が不可能である可能性があるが、化学療法を必要とする症例においては、術前薬物療法は依然として許容可能な選択肢である。これは、治療に良好な反応を示し、腋窩リンパ節郭清を回避できる可能性がある患者（T2, N1, M0、T3, N0, M0、T3, N1, M0）に対して有益となりうる。ST-1を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前薬物療法：乳房および腋窩の評価

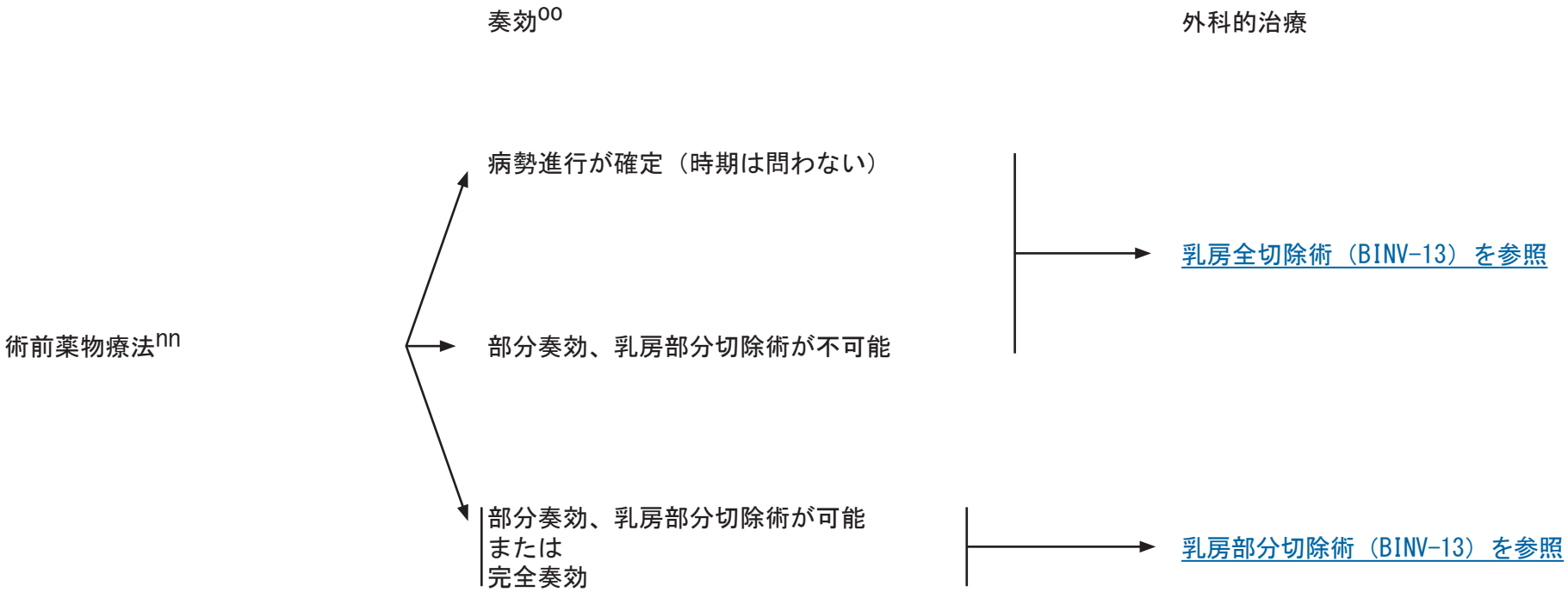


[ll] 根治目的の手術時に生検陽性のリンパ節が切除されたことが確認できるように、採取した腋窩リンパ節への入れ墨またはクリップによるマーキングを考慮すべきである。

[mm] 術前薬物療法の前にリンパ節転移陽性と判定された患者では、術前薬物療法の後に施行されたSLNBの偽陰性率が10%を超える。二重のトレーサーを用いて生検したリンパ節をマーキングして切除したことの記録を残すことにより、またセンチネルリンパ節を3個以上切除することにより、この偽陰性率を改善することができる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前薬物療法：外科的治療



nn 術前薬物療法の原則（BINV-L）を参照のこと。

oo 乳癌の原発巣および領域リンパ節における術前薬物療法の効果を正確に評価するのは難しく、その評価には身体診察に加えて、最初の病期診断時に異常がみられた画像検査（マンモグラフィおよび/または乳房MRI）を含めるべきである。手術前の画像検査法の選択は、集学的チームによって決定されるべきである。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前薬物療法：術後療法

外科的治療

術後療法

乳房全切除術および外科的腋窩病期診断[m]＋再建術[q]（任意）

- 術前に完了していない場合は、予定の化学療法を完了させる。
- タキサン系薬剤、アルキル化薬およびアントラサイクリン系薬剤をベースとする化学療法による標準的な術前療法後に浸潤癌が残存するトリプルネガティブ乳癌患者では、カペシタビンによる術後療法を考慮。

および

- 術後放射線療法[s]は、診断時の化学療法前の腫瘍の特徴からの最も進んだ病期と化学療法後の病理学的検査の結果に基づく。
  - ▸乳房全切除術後[s]：
    - ◊ 臨床的N1、ypN0例には、胸壁＋鎖骨下領域、鎖骨上領域、内胸リンパ節、およびリスクのある全腋窩領域に対する放射線療法を強く考慮。
    - ◊ 化学療法後も陽性のすべての腋窩リンパ節に対して、必要に応じて胸壁＋鎖骨下領域、鎖骨上領域、内胸リンパ節、およびリスクのある全腋窩領域に対する放射線療法。
  - ▸乳房部分切除術後[s]：
    - ◊ 乳房部分切除術後の術後放射線療法は全乳房に対して適応となる。
    - ◊ 臨床的N1、ypN0例には、全乳房＋鎖骨下領域、鎖骨上領域、内胸リンパ節、およびリスクのある全腋窩領域に対する放射線療法を強く考慮。
    - ◊ 化学療法後も陽性のすべての腋窩リンパ節に対して、必要に応じて全乳房＋鎖骨下領域、鎖骨上領域、内胸リンパ節、およびリスクのある全腋窩領域に対する放射線療法。

外科的腋窩病期診断を伴う乳房部分切除術[m]

および

- ERおよび/またはPR陽性の場合、術後内分泌療法[bb]（カテゴリー1）

および

- HER2陽性の場合、トラスツズマブ（カテゴリー1）±ペルツズマブによる最長1年間の抗HER2療法を完遂。必要であれば、抗HER2療法は放射線療法および内分泌療法と同時に施行してもよい[ff]。

サーベイランス/フォローアップ（BINV-16）を参照

[m] 外科的腋窩病期診断（BINV-D）を参照のこと。
[q] 術後乳房再建の原則（BINV-H）を参照のこと。
[s] 放射線療法の原則（BINV-I）を参照のこと。
[bb] 術後療法としての化学療法と内分泌療法は、化学療法に続いて内分泌療法という順序で逐次的に施行すべきである。現時点で得られているデータによると、放射線療法と内分泌療法の逐次または同時併用は許容できることが示唆される。術後内分泌療法（BINV-J）および術前/術後療法のレジメン（BINV-K）を参照のこと。
[ff] 再発リスクが高いと考えられるHR陽性HER2陽性例には、トラスツズマブを含む術後療法に続いてneratinibによる更なる術後療法を考慮する。ペルツズマブの投与を受けた患者におけるneratinibによる追加治療の利益や毒性については不明である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
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手術不能または局所進行乳癌（非炎症性）に対する術前薬物療法

臨床病期

T0, N2, M0
T1, N2, M0
T2, N2, M0
T3, N2, M0

T3, N1, M0の患者、BINV-10を参照

T4, N0, M0
T4, N1, M0
T4, N2, M0

Any T, N3, M0

精査

- 病歴聴取と身体診察
- 診断的両側マンモグラフィ、必要に応じて超音波検査
- 病理所見の再検討[b]
- 腫瘍のER/PRおよびHER2の発現状況を判定[c]
- 遺伝性乳癌のリスクが高い患者の場合は遺伝カウンセリング[d]
- 乳房MRI[e]（任意）、マンモグラフィで発見されない腫瘍に特に注意
- 閉経前であれば妊孕性の懸念に関するカウンセリング；妊娠可能なすべての女性で妊娠検査[f]
- 精神的苦痛の評価[g]

以下の追加検査を考慮：

- 血算
- 肝機能検査およびアルカリホスファターゼを含む生化学検査（comprehensive metabolic panel）
- 胸部の画像診断用造影CT
- 腹部±骨盤の画像診断用造影CTまたは造影MRI
- 骨シンチグラフィまたはSodium Fluoride PET/CT[i]（カテゴリー2B）
- FDG PET/CT[j,k]（任意）

→ 手術不能または局所進行乳癌（非炎症性）に対する術前薬物療法（BINV-15）を参照

[b] 当委員会は、すべての浸潤性および非浸潤性乳癌の病理報告についてCollege of American Pathologists Protocolを支持している。http://www.cap.org
[c] HER2検査の原則（BINV-A）を参照のこと。
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[i] FDG PET/CTを施行して、PETとCTの両要素から骨転移が明白に示された場合には、骨シンチグラフィまたはSodium Fluoride PET/CTは必要ないと考えられる。
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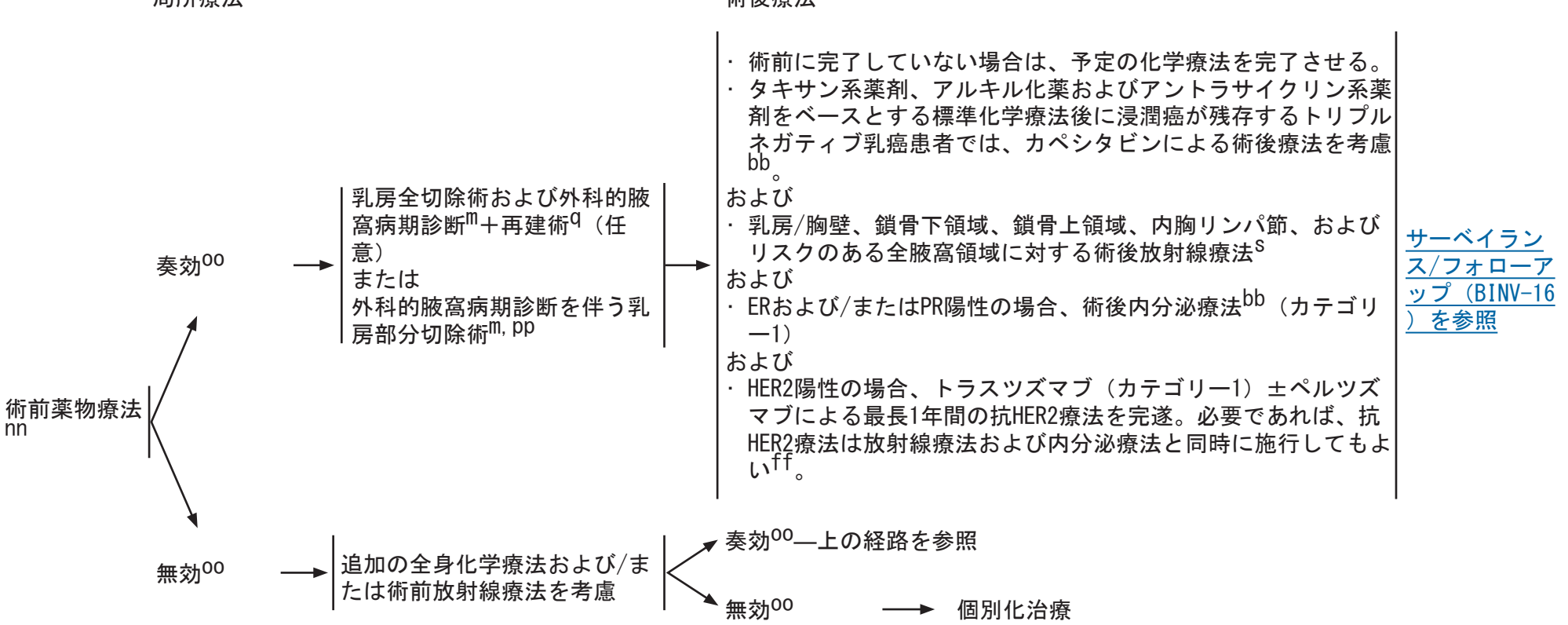
手術不能または局所進行乳癌（非炎症性）に対する術前薬物療法



q 術後乳房再建の原則（BINV-H）を参照のこと。
m 外科的腋窩病期診断（BINV-D）を参照のこと。
s 放射線療法の原則（BINV-I）を参照のこと。
bb術後療法としての化学療法と内分泌療法は、化学療法に続いて内分泌療法という順序で逐次的に施行すべきである。現時点で得られているデータによると、放射線療法と内分泌療法の逐次または同時併用は許容できることが示唆される。術後内分泌療法（BINV-J）および術前/術後療法のレジメン（BINV-K）を参照のこと。
ff 再発リスクが高いと考えられるHR陽性HER2陽性例には、トラスツズマブを含む術後療法に続いてneratinibによる更なる術後療法を考慮する。ペルツズマブの投与を受けた患者におけるneratinibによる追加治療の利益や毒性については不明である。
nn術前薬物療法の原則（BINV-L）を参照のこと。

oo乳癌の原発巣および領域リンパ節における術前薬物療法の効果を正確に評価するのは難しく、その評価には身体診察に加えて、最初の病期診断時に異常がみられた画像検査（マンモグラフィおよび/または乳房MRI）を含めるべきである。手術前の画像検査法の選択は、集学的チームによって決定されるべきである。
pp術前薬物療法の前に皮膚および/または胸壁浸潤を認める患者（T4、非炎症性）では、局所再発リスクについての集学的評価に基づき、慎重に選択した患者に対して乳房温存療法を行ってもよい。乳房温存に対する標準的な禁忌（BINV-Gを参照）に加え、乳房温存療法の除外基準には、術前薬物療法前の炎症性（T4d）乳癌と術前薬物療法後の皮膚浸潤の不完全な消退が含まれる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

サーベイランス/フォローアップ

- 病歴聴取と身体診察、5年間は臨床的必要性に応じて年1～4回、以後は年1回
- 家族歴の変化に対する定期的なスクリーニングと必要に応じて遺伝カウンセリングへの紹介；NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照
- リンパ浮腫の管理を目的とする教育、モニタリングおよび紹介
- 12ヵ月毎のマンモグラフィ[qq]
- 再建乳房のルーチンの画像検査は適応とならない。
- 再発を示唆する臨床的な徴候や症状を認めない場合には、転移に対するスクリーニングのための臨床検査および画像検査は適応とならない。
- タモキシフェン投与中の女性：12ヵ月毎に婦人科検診（子宮が切除されている場合を除く）
- アロマターゼ阻害薬の投与中であるか治療による卵巣不全が生じている女性には、ベースライン時とその後は定期的に骨密度を測定して、骨の健康状態をモニタリングすべきである[rr]
- 術後内分泌療法に対するアドヒアランスの評価および促進
- 活動的な生活様式、健康的な食事、飲酒の制限、ならびに理想体重（BMIが20～25）の達成および維持によって、乳癌の予後は至適となることがエビデンスから示唆されている。
- NCCN Guidelines for Survivorshipを参照

再発（BINV-17）を参照

[qq]年1回のマンモグラフィは、乳房温存手術および放射線療法を受けた乳癌患者のサーベイランスに適切な頻度であり、これより短い間隔での画像検査に明確な利点はないことが研究により示されている。放射線療法完了の6～12ヵ月経過後からマンモグラフィによる年1回のサーベイランスを開始すべきである。身体診察またはサーベイランスの画像検査で疑わしい所見を認めた場合は、マンモグラフィの実施間隔を短くするのが妥当である。

[rr]乳癌女性における骨粗鬆症または骨量減少治療へのエストロゲン、プロゲステロンまたは選択的エストロゲン受容体修飾剤の使用は勧められない。ビスホスフォネート系薬剤（経口/静注）またはデノスマブの使用は、骨密度の維持または改善の普段として許容可能であり、術後内分泌療法を受けている閉経後（自然または人工）患者の骨折リスクを低下させる。いずれの治療法も至適投与期間は確立されていない。3年を超える期間は不明である。骨粗鬆症に対する治療の継続期間について考慮すべき因子としては、骨密度、治療に対する反応、持続的な骨量減少または骨折の危険因子などがある。ビスホスフォネート系薬剤またはデノスマブによる治療を受ける女性は、治療開始前に予防歯科検診を受けるべきであり、カルシウムおよびビタミンDサプリメントを服用すべきである。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）

臨床病期　　精査

再発
または
IV期（M1）

- 病歴聴取と身体診察
- 治療目標について話し合い、共同での意思決定を採用し、ケアの経過を記録する
- 血算
- 肝機能検査およびアルカリホスファターゼを含む生化学検査（comprehensive metabolic panel）
- 胸部の画像診断用造影CT
- 腹部±骨盤の画像診断用造影CTまたは造影MRI
- CNS症状が疑われる場合は脳の造影MRI
- 背部痛または脊髄圧迫の症状がある場合は脊椎の造影MRI
- 骨シンチグラフィまたはSodium Fluoride PET/CT[i]（カテゴリー2B）
- FDG PET/CT[k,ss]（任意）
- 症状のある骨および骨シンチグラフィで異常がみられた荷重長幹骨のX線
- 初回再発例では生検を行うべきである
- 転移巣におけるER/PRおよびHER2の発現状況を判定[c,tt,uu]
- 単剤療法に適格なHER2陰性例には、生殖細胞系*BRCA 1/2*変異の検査を強く考慮
- 遺伝性乳癌のリスクが高い患者の場合は遺伝カウンセリング[d]

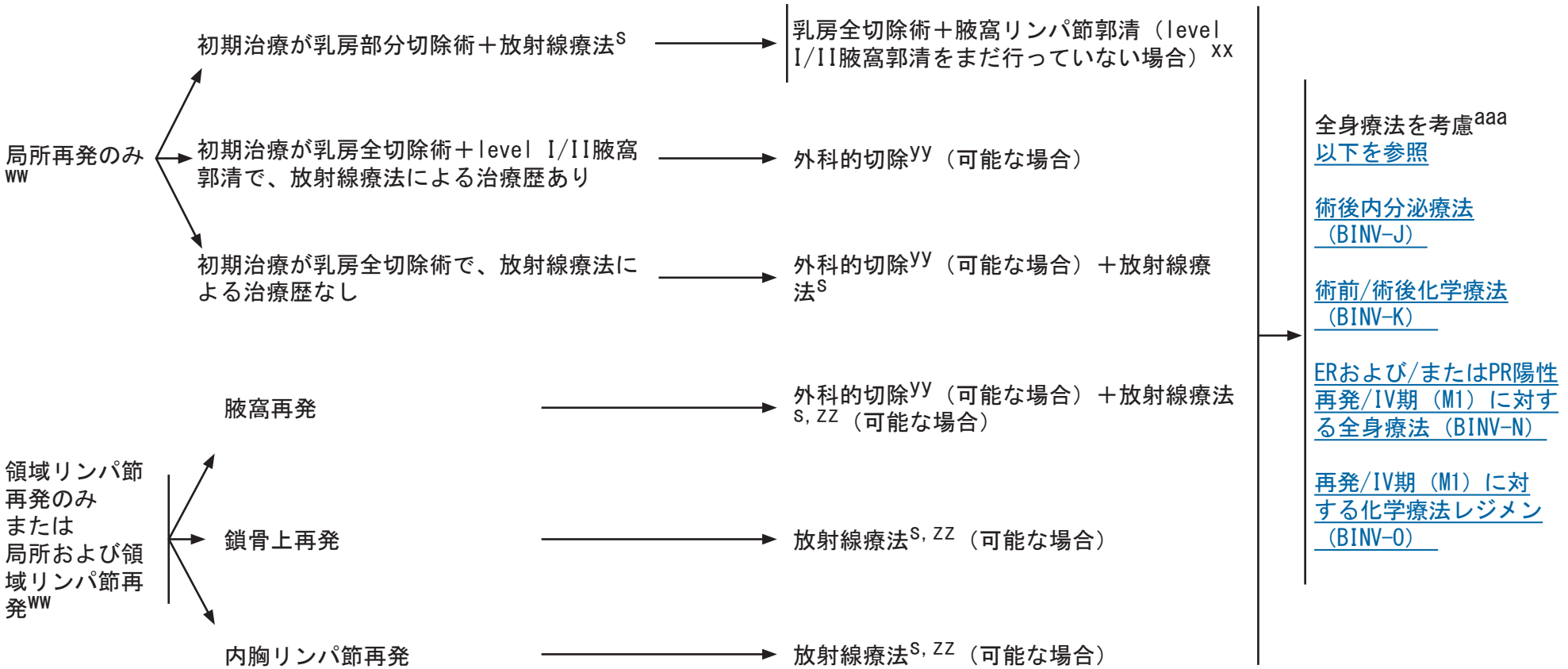
→ 局所および領域リンパ節再発の治療（BINV-18）を参照
および
支持療法[vv]

→ 再発/IV期（M1）の全身療法（BINV-19）を参照
および
支持療法[vv]

[c] HER2検査の原則（BINV-A）を参照のこと。
[d] NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。
[i] FDG PET/CTを施行して、PETとCTの両要素から骨転移が明白に示された場合には、骨シンチグラフィまたはSodium Fluoride PET/CTは必要ないと考えられる。
[k] FDG PET/CTは、標準的な病期診断検査に加えて用いる場合、局所進行乳癌において疑われていない領域リンパ節病変や遠隔転移を同定するのにも有用となりうる。
[ss] FDG PET/CTは診断目的のCTと同時に施行できる。FDG PET/CTは、標準的な病期診断検査では結果が曖昧であるか疑わしい状況で最も有用となる（特に局所進行例または転移例の場合）。
[tt] ERおよび/またはPRについて偽陰性となる場合や、原発巣と転移巣でERおよび/またはPRの結果が一致しない場合もある。そのため、内臓以外への転移または無症候性の内臓転移を有する患者、特にホルモン受容体陽性の腫瘍を予測させる臨床的特徴（無病期間が長い、再発部位が限定的、病変の進行が遅い、高齢など）を有する患者では、内分泌療法を考慮してもよい。
[uu] 生検を安全に施行できず、再発が強く示唆される臨床所見を認めた場合は、原発巣のER/PR/HER2の発現状況に応じて治療を開始してもよい。
[vv] NCCN Guidelines for Supportive Careを参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

局所および領域リンパ節再発の治療



S 放射線療法の原則（BINV-I）を参照のこと。

WW 乳癌再発の管理で至適な転帰を達成するために可能な選択肢をすべて考慮するには、集学的アプローチが特に重要となる。

XX センチネルリンパ節生検（SNB）を受けたことのある女性で、乳房温存手術後に局所再発が認められた場合、再度SNBを行うことは技術的に可能であると考えられる。再施行する場合のSNBの精度は証明されておらず、乳房全切除術後のSNBの再施行による予後予測上の意義は不明であり、その使用は勧められない。

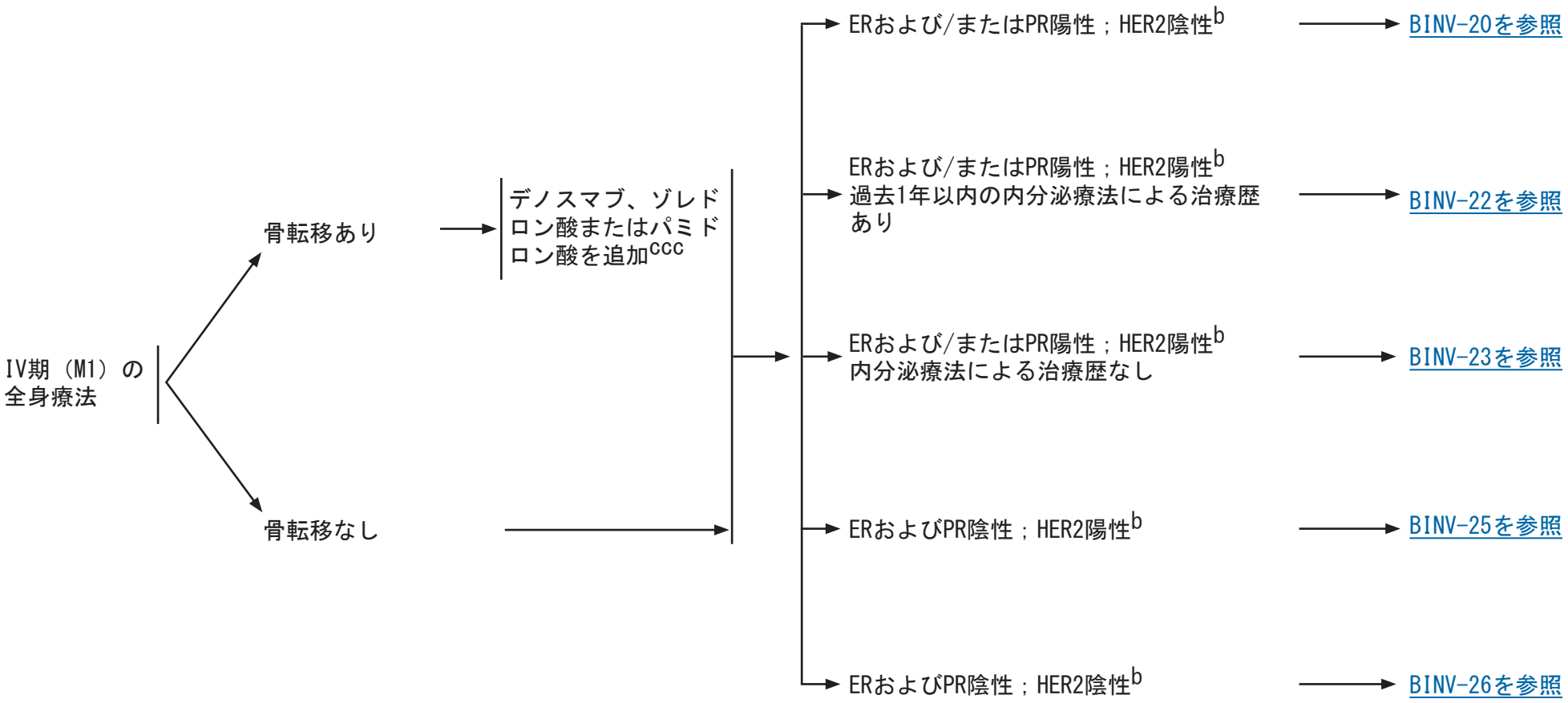
YY 技術的に切除不能であれば、全身療法で最大の奏効を得た後で、可能であれば切除する方針を考慮する。

ZZ 局所・領域リンパ節再発の治療として放射線療法を実施する場合、その領域へのすべての照射歴を考慮し、これまでの照射線量および予定される照射線量の合計による正常組織への晩期毒性リスクを考慮しなければならない。

aaa 詳細については、考察の節を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）の全身療法



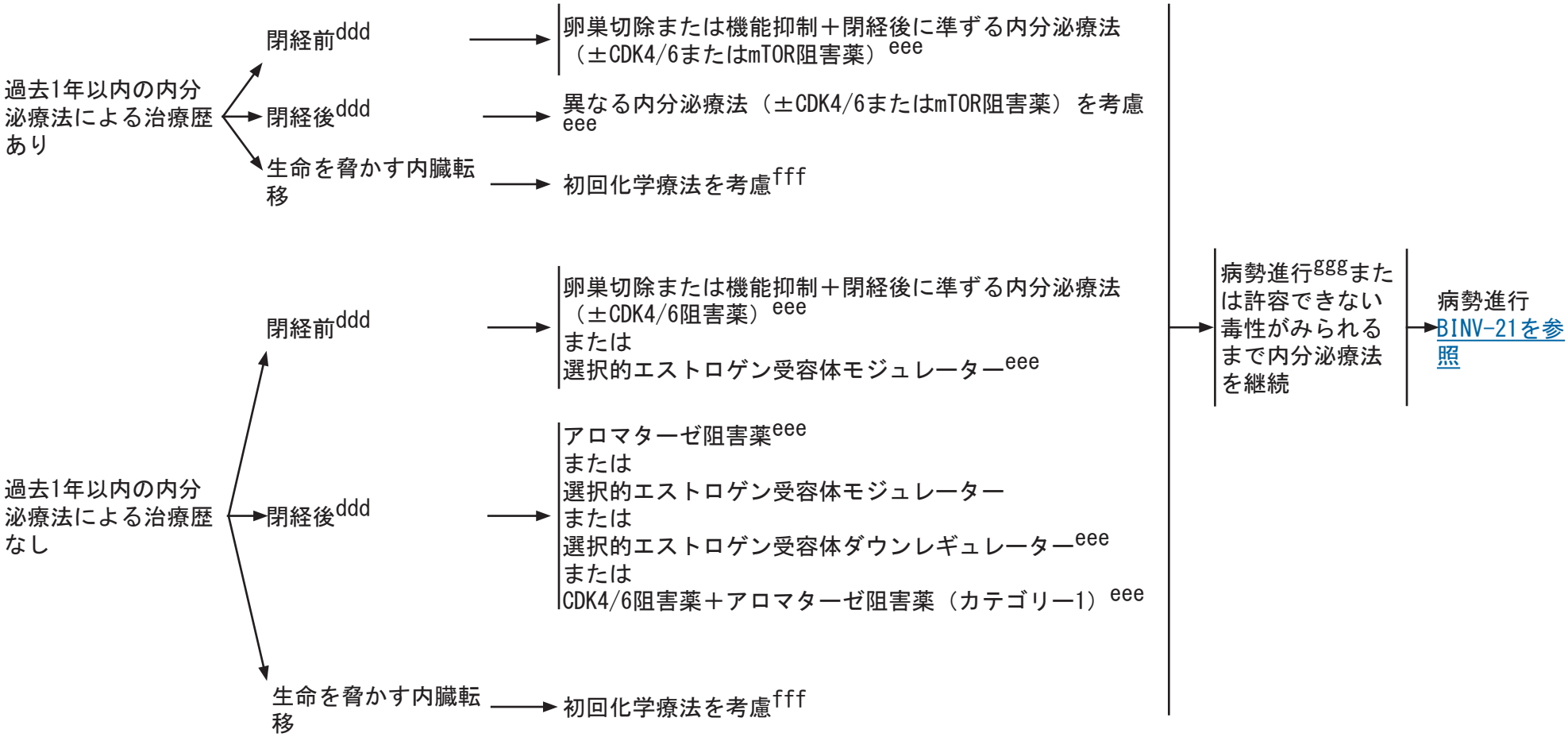
c HER2検査の原則（BINV-A）を参照のこと。

bbb 初発時からIV期（M1）の患者における原発巣の外科的切除の役割および施行時期については、現在も検討が進められており、個々の患者毎に判断しなければならない。初回の全身療法で効果が得られた一部の患者では、局所乳房手術および/または放射線療法の施行が妥当である。

ccc 骨転移があり、3ヵ月以上の生存期間が予測され、腎機能が十分である場合、化学療法または内分泌療法に加えて、デノスマブ、ゾレドロン酸またはパミドロン酸（いずれも、カルシウムおよびビタミンD補充を併用）を投与する（カテゴリー1）。この治療を開始する前に、患者は歯科検診を受けべきである。ゾレドロン酸の至適投与スケジュールは、月1回 × 12回、その後は年4回である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

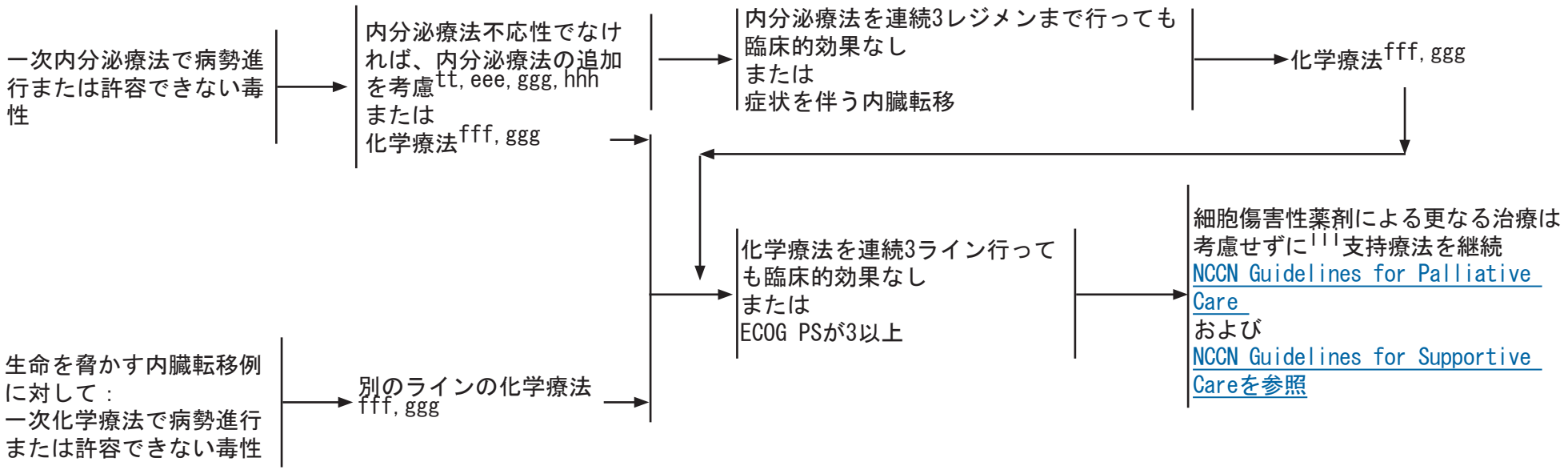
再発/IV期（M1）の全身療法
ERおよび/またはPR陽性；HER2陰性[c]



c HER2検査の原則（BINV-A）を参照のこと。
ddd 閉経の定義（BINV-M）を参照のこと。
eee ERおよび/またはPR陽性再発/IV期（M1）に対する全身療法（BINV-N）を参照のこと。
fff 再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。
ggg 遠隔転移のモニタリングの原則（BINV-P）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

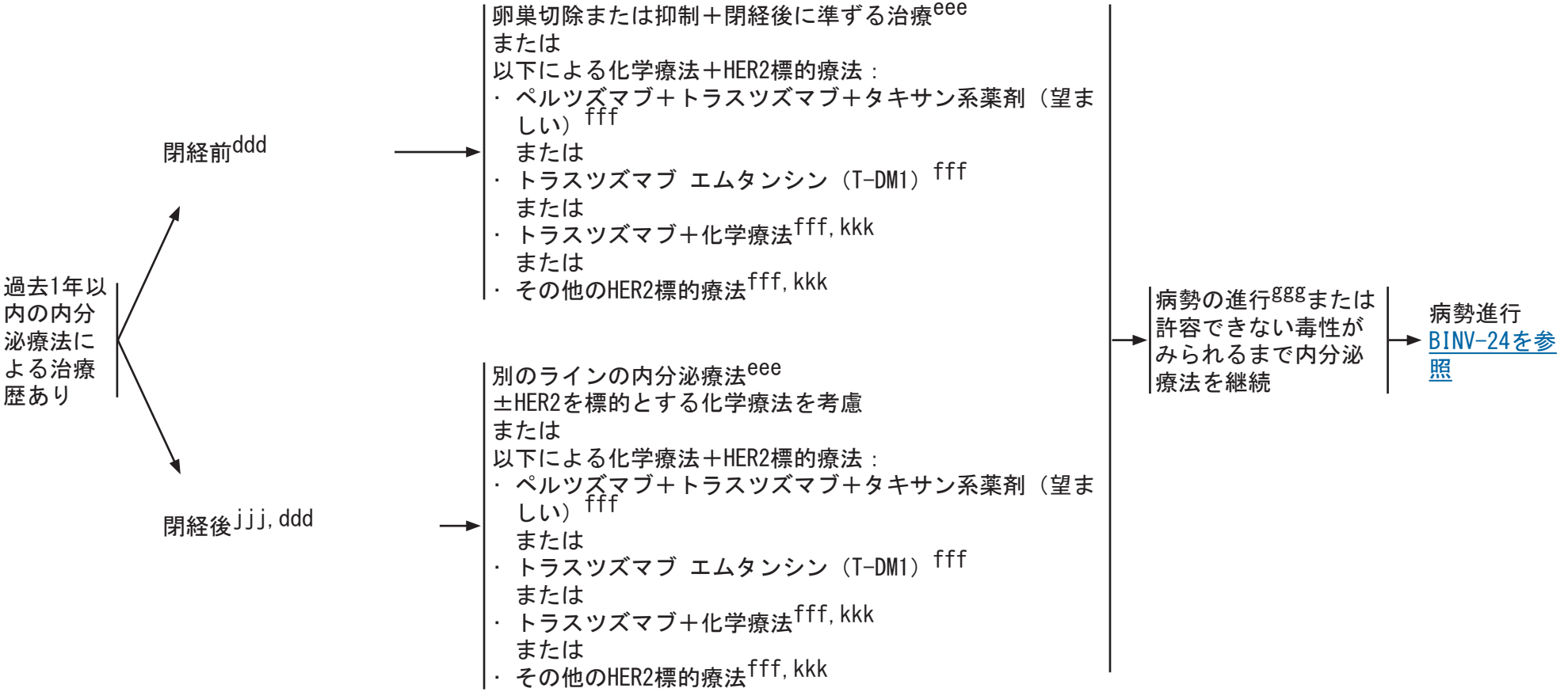
再発/IV期（M1）の全身療法
ERおよび/またはPR陽性；HER2陰性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。
[tt] ERおよび/またはPRについて偽陰性となる場合や、原発巣と転移巣でERおよび/またはPRの結果が一致しない場合もある。そのため、内臓以外への転移または無症候性の内臓転移を有する患者、特にホルモン受容体陽性の腫瘍を予測させる臨床的特徴（無病期間が長い、再発部位が限定的、病変の進行が遅い、高齢など）を有する患者では、内分泌療法を考慮してもよい。
[eee] ERおよび/またはPR陽性再発/IV期（M1）に対する全身療法（BINV-N）を参照のこと。
[fff] 再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。
[ggg] 遠隔転移のモニタリングの原則（BINV-P）を参照のこと。
[hhh] CDK4/6阻害薬による治療中に進行がみられた場合については、CDK4/6阻害薬を含む別のレジメンによる更なる治療の実施を裏付けるデータはない。同様に、エベロリムスを含むレジメンによる治療中に病勢がみられた場合についても、エベロリムスを含む別のレジメンによる更なる治療の実施を裏付けるデータもない。
[iii] 全身状態（PS）が不良の患者では、化学療法を追加することで潜在的な副作用が臨床的利益を上回る可能性がある。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）の全身療法
ERおよび/またはPR陽性；HER2陽性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。
[ddd] 閉経の定義（BINV-M）を参照のこと。
[eee] ERおよび/またはPR陽性再発/IV期（M1）に対する全身療法（BINV-N）を参照のこと。
[fff] 再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。
[ggg] 遠隔転移のモニタリングの原則（BINV-P）を参照のこと。
[jjj] 限られた研究結果から、ER陽性HER2陽性の乳癌閉経後患者においてアロマターゼ阻害薬にトラスツズマブまたはラパチニブを追加することによる無進行生存期間の改善が示されている。しかしながら、全生存期間の改善は実証されていない。
[kkk] トラスツズマブのアントラサイクリン系薬剤との併用については、重大な心毒性との関連が認められる。トラスツズマブおよびペルツズマブとアントラサイクリン系薬剤との併用は避けるべきである

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）の全身療法
ERおよび/またはPR陽性；HER2陽性[c]

過去1年以内の内分泌療法による治療歴なし

閉経前[ddd] →
- 卵巣切除または抑制＋閉経後に準ずる治療[eee]
  または
- 選択的エストロゲン受容体モジュレーター[eee]±HER2標的療法
  または
- 以下による化学療法＋HER2標的療法：
  - ペルツズマブ＋トラスツズマブ＋タキサン系薬剤（望ましい）[fff,kkk]
    または
  - トラスツズマブ エムタンシン（T-DM1）[fff,kkk]
    または
  - トラスツズマブ＋化学療法[fff,kkk]
    または
  - その他のHER2標的療法[fff,kkk]

閉経後[jjj,ddd] →
- アロマターゼ阻害薬[eee]±HER2標的療法
  または
- 選択的エストロゲン受容体モジュレーター±HER2標的療法
  または
- 選択的エストロゲン受容体ダウンレギュレーター[eee] ±HER2標的療法
  または
- 以下による化学療法＋HER2標的療法：
  - ペルツズマブ＋トラスツズマブ＋タキサン系薬剤（望ましい）[fff]
    または
  - トラスツズマブ エムタンシン（T-DM1）[fff]
    または
  - トラスツズマブ＋化学療法[fff,kkk]
    または
  - その他のHER2標的療法[fff,kkk]

→ 病勢の進行[ggg]または許容できない毒性がみられるまで治療を継続 → 病勢進行 → BINV-24を参照

[c] HER2検査の原則（BINV-A）を参照のこと。
[ddd] 閉経の定義（BINV-M）を参照のこと。
[eee] ERおよび/またはPR陽性再発/IV期（M1）に対する全身療法（BINV-N）を参照のこと。
[fff] 再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。
[ggg] 遠隔転移のモニタリングの原則（BINV-P）を参照のこと。
[jjj] 限られた研究結果から、ER陽性HER2陽性の乳癌閉経後患者においてアロマターゼ阻害薬にトラスツズマブまたはラパチニブを追加することによる無進行生存期間の改善が示されている。しかしながら、全生存期間の改善は実証されていない。
[kkk] トラスツズマブのアントラサイクリン系薬剤との併用については、重大な心毒性との関連が認められる。トラスツズマブおよびペルツズマブとアントラサイクリン系薬剤との併用は避けるべきである

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
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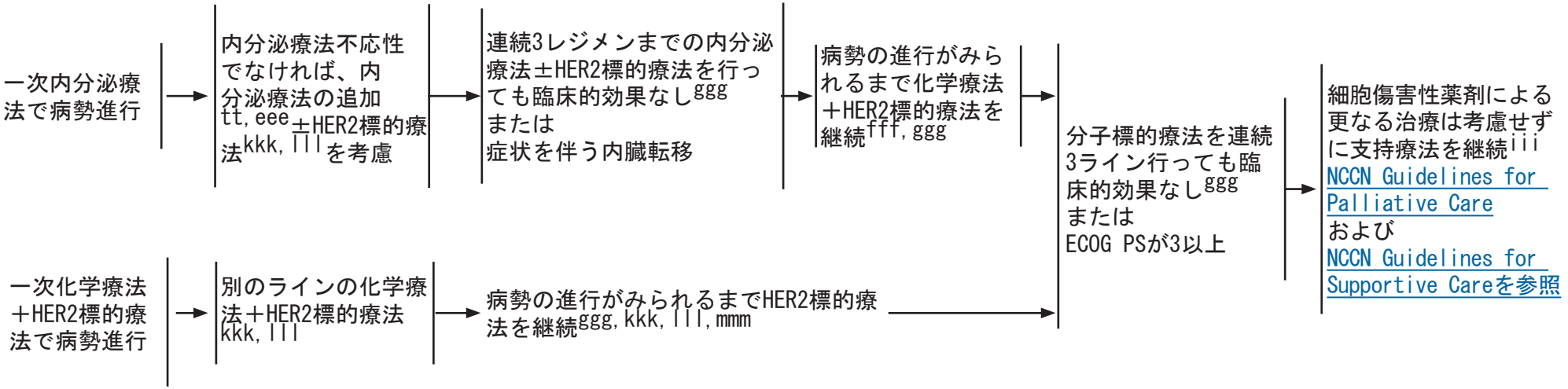
再発/IV期（M1）の全身療法
ERおよび/またはPR陽性；HER2陽性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。

[tt] ERおよび/またはPRについて偽陰性となる場合や、原発巣と転移巣でERおよび/またはPRの結果が一致しない場合もある。そのため、内臓以外への転移または無症候性の内臓転移を有する患者、特にホルモン受容体陽性の腫瘍を予測させる臨床的特徴（無病期間が長い、再発部位が限定的、病変の進行が遅い、高齢など）を有する患者では、付随する毒性の低い内分泌療法を考慮してもよい。

[eee] ERおよび/またはPR陽性再発/IV期（M1）に対する全身療法（BINV-N）を参照のこと。

[fff] 再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。

[ggg] 遠隔転移のモニタリングの原則（BINV-P）を参照のこと。

[iii] 全身状態（PS）が不良の患者では、化学療法を追加することで潜在的な副作用が臨床的利益を上回る場合がある。

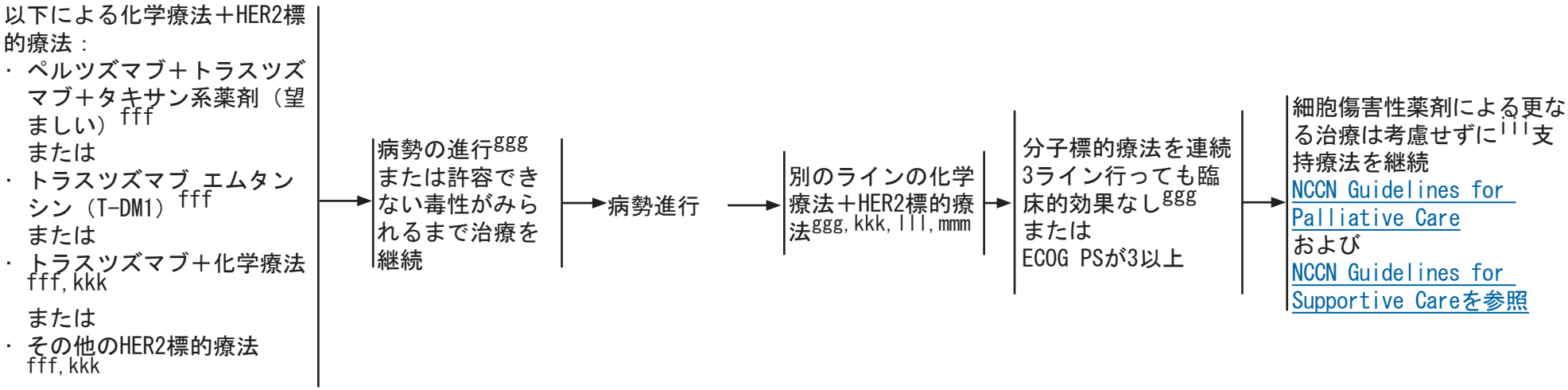
[kkk] トラスツズマブのアントラサイクリン系薬剤との併用については、重大な心毒性との関連が認められる。トラスツズマブおよびペルツズマブとアントラサイクリン系薬剤との併用は避けるべきである

[lll] 過去にペルツズマブの併用なしで化学療法＋トラスツズマブによる治療を受けた患者では、細胞傷害性薬剤（ビノレルビンやタキサン系薬剤など）の併用の有無にかかわらず、トラスツズマブとペルツズマブの両方を含む1ラインの治療を考慮してもよい。抗HER2療法のための理想的な逐次併用の投与戦略を確立するには、更なる研究が必要である。

[mmm] 転移乳癌に対するHER2を標的とする一次化学療法で病勢進行となった後にはHER2標的療法を継続する。疾患を長期管理できている患者におけるトラスツズマブの至適投与期間は不明である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）の全身療法
ERおよび/またはPR陰性；HER2陽性[c]



[c] HER2検査の原則（BINV-A）を参照のこと。
[fff] 再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。
[ggg] 遠隔転移のモニタリングの原則（BINV-P）を参照のこと。
[iii] 全身状態（PS）が不良の患者では、化学療法を追加することで潜在的な副作用が臨床的利益を上回る場合がある。
[kkk] トラスツズマブのアントラサイクリン系薬剤との併用については、重大な心毒性との関連が認められる。トラスツズマブおよびペルツズマブとアントラサイクリン系薬剤との併用は避けるべきである
[lll] 過去にペルツズマブの併用なしで化学療法＋トラスツズマブによる治療を受けた患者では、細胞傷害性薬剤（ビノレルビンやタキサン系薬剤など）の併用の有無にかかわらず、トラスツズマブとペルツズマブの両方を含む1ラインの治療を考慮してもよい。抗HER2療法のための理想的な逐次併用の投与戦略を確立するには、更なる研究が必要である。
[mmm] 転移乳癌に対するHER2を標的とする一次化学療法で病勢進行となった後にはHER2標的療法を継続する。疾患を長期管理できている患者におけるトラスツズマブの至適投与期間は不明である。

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再発/IV期（M1）の全身療法
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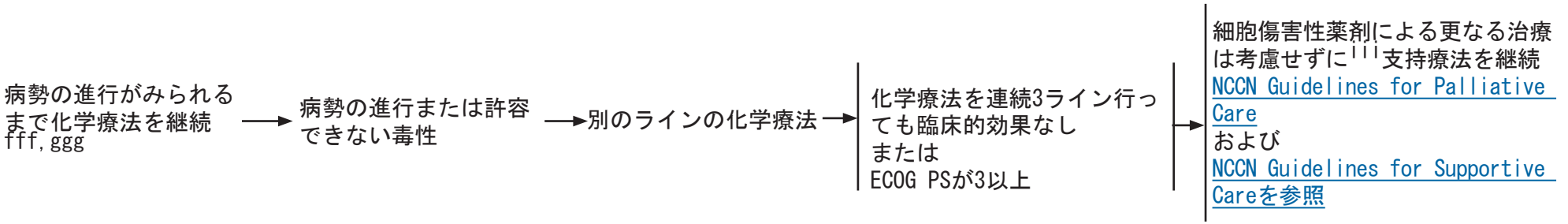

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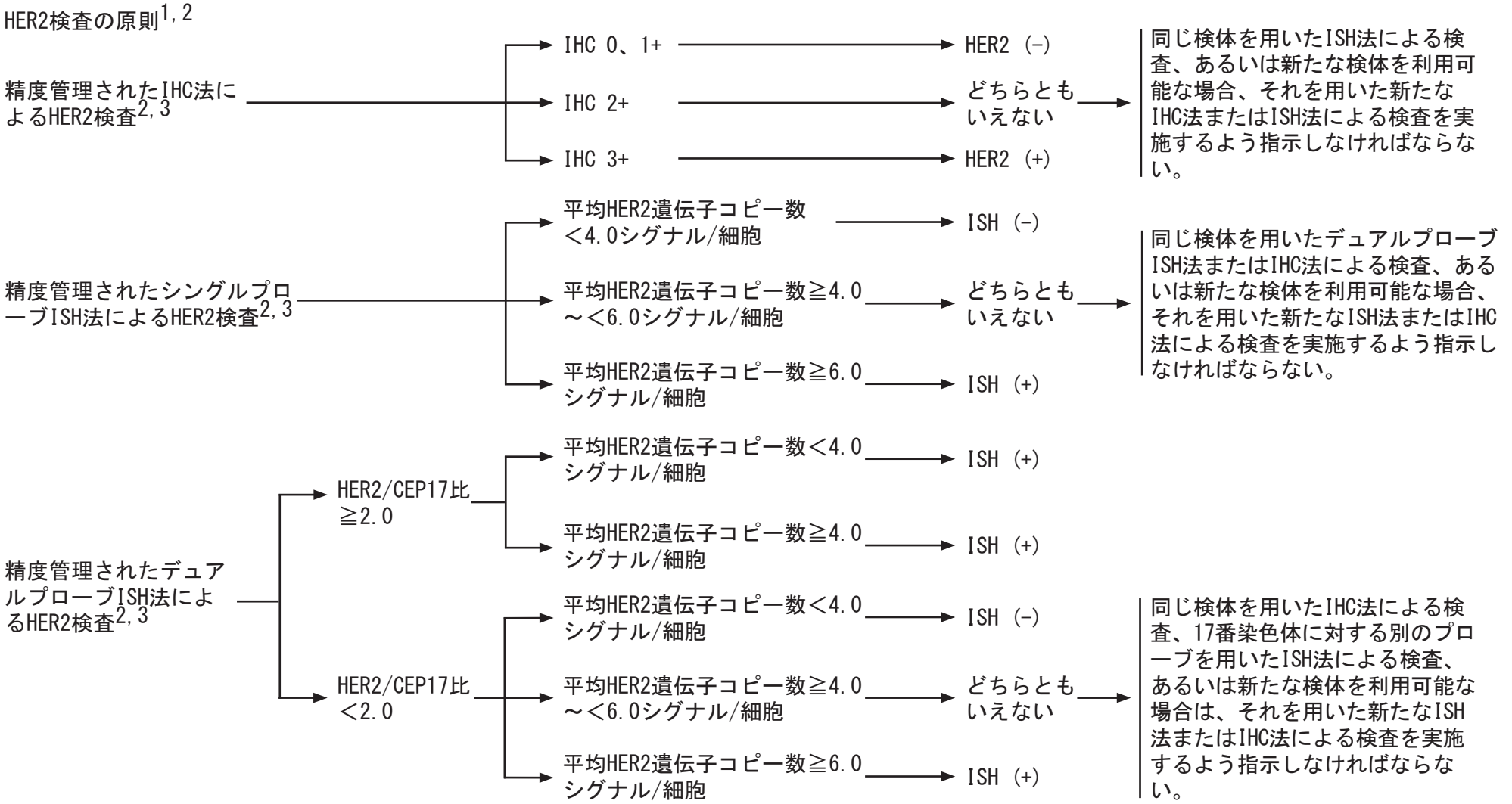


1 NCCNはASCO/CAP HER2検査ガイドラインを承認している。「HER2検査の原則」は、以下から許諾を得て一部修正したものである：Wolff AC, Hammond EH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013;31:3997-4013.

2 検査室は、HER2検査の品質保証認定プログラムに参加しなければならない。さもなければ、組織検体を認定された検査室に送付し、検査を受けること。医療システムおよび医療提供者は、最高品質の検査が確実に行われるよう協力しなければならない。

3 トラスツズマブ術後療法試験のエビデンスから、ISH法またはIHC法によるHER2検査は、HER2標的療法による臨床効果を予測する有用性が同程度であることが示されている。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

乳房MRI検査の原則

乳癌リスクの高い女性に対するスクリーニングMRIの適応については、NCCN乳癌スクリーニング・診断ガイドラインを参照のこと。

人員、施設、機器

- 乳房MRI検査は静注造影剤を用いて実施し、乳房画像診断の専門チームが集学的治療チームと協力して実施するべきである。
- 乳房MRI検査には専用の乳房コイルと、画像を診断するための最適な手順のタイミングやその他の技術的詳細に精通した乳房画像診断を専門とする放射線科医が必要である。画像診断センターは、MRIガイド下針生検の検体採取および/またはMRIで検出した所見の画像ガイド下位置確認を実施できなければならない。

臨床適応症および臨床適用

- 癌の範囲または同側乳房における多病巣性または多中心性癌の有無を明らかにするための病期診断に利用することも、初回診断時に対側乳癌のスクリーニングとして使用することもできる（カテゴリー2B）。局所療法の意思決定を容易にするためのMRIの使用が、局所再発を減らし生存期間を延長したことを示す明らかな根拠はない[1]。
- 術前薬物療法の前後に病変範囲、治療効果、乳房温存療法の可能性を明らかにするために乳癌の評価を行う上でも有用となりうる。
- 腋窩リンパ節に腺癌がみられ、原発巣が不顕性（または不特定）の女性、パジェット病の女性またはマンモグラフィ、超音波検査、身体診察で浸潤性小葉癌が不確定（または不十分）な女性における原発巣の同定に有用な場合がある。
- 乳房MRIでは偽陽性所見がよくみられる。MRI所見のみに基づいて外科的な判断を下してはならない。乳房MRIで特定された問題領域における組織採取を追加することが推奨される。
- 乳癌の既往がある女性の追跡スクリーニングにおけるMRIの有用性は明らかになっていない。一般的に、遺伝による乳癌感受性に関連するリスクを有する場合など、主に家族歴に依存したモデルに基づき、二次性の原発性乳癌を生じる生涯リスクが20%を超える女性に限って、考えるべきである。

1 Houssami N, Ciatto S, Macaskill P, et al.Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer.J Clin Oncol 2008;26:3248-3258.

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

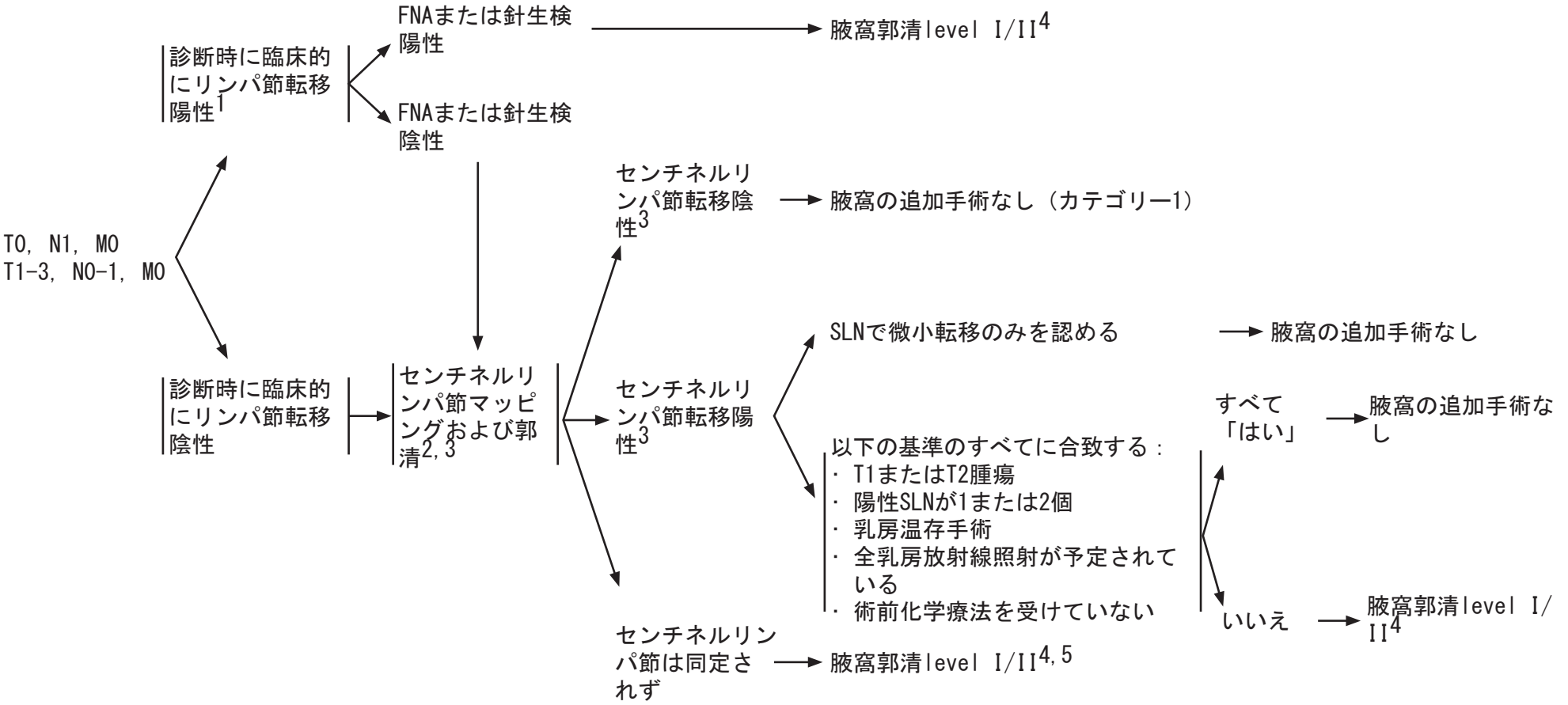
妊孕性および避妊

NCCN Guidelines for Adolescent and Young Adult Oncologyを参照

- 閉経前患者全員に、化学療法により妊孕性が影響を受ける可能性のあることを通知し、将来妊娠を希望するか否かを尋ねておく必要がある。将来の妊娠を希望する患者には、化学療法および/または内分泌療法開始前に不妊治療専門医を紹介し、（治療の緊急性、種類、および順序を規定する）患者の特質、病期、および生物学的特徴に基づき選択肢を話し合うべきである。妊孕性の保存に許される時期および期間、卵子および胚の凍結保存に加え今後の進展が見込まれる技術を含めた選択肢、ならびに乳癌治療終了後の正常妊娠の可能性についても話し合うべきである。
- 化学療法の施行中または施行後には無月経となることが多いが、**35**歳未満の女性の大多数では、術後化学療法の終了後**2**年以内に月経が再開するようである。
- 月経と妊孕性は必ずしも関連しない。特に患者がタモキシフェンを服用している場合、規則的な月経がないことは、必ずしも妊孕性がないことを暗示しない。逆に、月経があっても、妊孕性は保証されない。化学療法後の妊孕性の維持に関するデータは限られている。
- 放射線療法、化学療法または内分泌療法による治療期間中は、患者は妊娠してはならない。
- データは限られているが、ホルモン剤による避妊法は（患者の癌のホルモン受容体状態とは無関係に）推奨されない。
- それに代わる避妊法として、避妊リング（IUD）、バリア法または将来妊娠する意思のない患者に対しては、卵管結紮もしくはパートナーの精管切除などが挙げられる。
- 複数のランダム化試験によって、ER陰性腫瘍を有する閉経前女性では術後化学療法中にGnRHアゴニストによる卵巣抑制を行うことで、卵巣機能を温存でき、化学療法により無月経となる可能性が低下することが示されている。
- 乳房温存療法後の授乳は禁忌ではない。しかし、温存された乳房で産生される母乳の量および質は不十分で、何らかの必要な栄養素が欠けているかもしれない。化学療法および内分泌療法を用いた積極的治療中の授乳は推奨されない。
- ER陽性患者での使用経験は少なく、妊孕性に対するGnRHアゴニストの保護効果については相反する結果が報告されている。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

外科的腋窩病期診断—T0，N1，M0；T1-3，N0-1，M0期



1 腋窩リンパ節郭清が必要かどうか決めるために、臨床的に転移陽性が疑われるリンパ節に対してFNAや針生検を用いて病理学的に転移陽性かどうかを確認することが考慮される。
2 センチネルリンパ節マッピングの注射は、腫瘍周囲、乳輪下または皮下に行う。
3 センチネルリンパ節転移の有無はリンパ節から複数の切片を作成しヘマトキシリン-エオジン（HE）染色を行うことで確定される。HE染色で転移の有無が確定できない場合は、サイトケラチンの免疫組織化学法（IHC法）を実施してもよい。臨床的意思決定においてリンパ節転移の有無を確定するためにサイトケラチンのIHC法をルーチンで使用することは推奨されない。
4 腋窩リンパ節病期診断（BINV-E）を参照のこと。
5 臨床的に腋窩リンパ節転移陰性で、乳房全切除術を受け放射線療法を予定している患者であれば、局所制御目的のlevel I/II腋窩リンパ節郭清を腋窩への放射線療法に変更してもよい。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

腋窩リンパ節病期診断

センチネルリンパ節生検を実施すべきであり、患者がセンチネルリンパ節生検の対象として適切であれば、腋窩リンパ節病期診断の望ましい方法である（BINV-Dを参照）。

腋窩リンパ節病期診断の実施により生存率が高まることを示す確定的データが存在しないため、特に予後良好と思われる腫瘍の患者、術後薬物療法および/または放射線療法の選択が影響を受けそうにないと思われる患者、高齢者、あるいは深刻な併存疾患がある患者では、腋窩リンパ節病期診断の実施は任意と考えてよい。

胸郭入口部へのlevel IIIの郭清は、level IIおよび/またはIIIに肉眼で転移巣が認められる場合に限るべきである。
level IIのリンパ節に肉眼的疾患を認めない場合は、リンパ節郭清に小胸筋内側縁から広背筋外側までで腋窩静脈より下の組織を含めるべきである（level I/II）。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

DCISおよび浸潤性乳癌に対する断端状態による推奨

- 乳房温存手術（Breast Conserving Surgery:BCS）で得られた手術標本のすべてについて断端評価を実施すべきである。最適な断端評価を行うためには以下の項目を含める必要がある：
  - 手術標本の方向性
  - 肉眼的および顕微鏡的断端状態の記述
  - 最も断端に近い癌巣から断端までの距離、その癌巣の方向性とタイプ（浸潤巣または非浸潤巣）。
- マンモグラフィで発見された微小石灰化を伴うDCISでは、断端および標本のX線写真の分析により完全切除を確認すべきである。切除が十分か否か不確実な場合は、必ず切除後マンモグラフィも行う。
- 当NCCN委員会は、SSO/ASTROの2014年I/II期浸潤癌に対する断端ガイドライン[1]およびSSO/ASTRO/ASCOの2016年DCISに対するガイドライン[2]による乳房温存療法後の断端陰性の定義を受け入れる。BCS後のI/II期浸潤癌の患者で、断端陽性は「ink on tumor」（断端に浸潤癌またはDCIS細胞を認める）として定義する。これらの患者では一般に更なる手術が必要であり、断端陰性を達成するために再切除または乳房全切除術のいずれかを行う。再切除が技術的に可能で、BCSにより「no ink on tumor（断端陰性）」が達成できるのであれば、最初の切除標本で断端陽性であった方向を切除するか、元の切除された部分の全周を再切除すればよい。III期浸潤癌の選択された患者では、BCSに適格な可能性がある。このような患者でも同様な定義を用いれば、断端状態を評価できる。

DCIS

- BCSと全乳房放射線照射（whole Brain Radiation Therapy:WBRT）による治療を受けたDCIS患者の切除断端に関した定量的な報告では、2mm以上の切除断端の患者は、断端距離が狭い切除断端陰性と比べて同側乳房再発（Ipsilateral Breast Tumor Recurrence:IBTR）のリスクが低くなるが、さらに転帰を改善しようと2mmを大幅に超える断端を確保するルーチン診療は、エビデンスにより支持されているわけではない。断端の近くに微小または巣状のDCIS病変のみが認められる場合は、個々の症例で再切除しないでおくかどうかの決定を臨床的に判断してもよい。
- 切除術のみ（WBRTなし）の治療を受けたDCIS患者では、断端の距離にかかわらず、事前に規定された低リスクの患者でさえ、切除術とWBRTによる治療よりもIBTRの割合がかなり高い。切除術のみの治療で至適な断端距離は不明であるが、一部のエビデンスで2mmを超える断端距離によりIBTRの割合が改善することが示唆されるため、2mm以上を確保すべきである。
- 浸潤病巣の大きさが1mm以下として定義される微小浸潤を伴うDCIS（DCIS-M）で、DCIS-Mの大部分がDCISによって構成され、また、この病変に対する全身療法については、浸潤癌よりもDCISに対する治療パターンが通常適用されていることを考慮すると、DCISの断端定義である至適断端距離（2mm超）を参考にすべきである。

続く

1 Moran MS, Schnitt SJ, Giuliano AE, et al.Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer.J Clin Oncol 2014 May 10;32(14):1507-15.

2 Morrow M, Van Zee KJ, Solin LJ, et al.Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ.J Clin Oncol 2016;34:4040-4046.

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

DCISおよび浸潤性乳癌に対する断端状態による推奨

浸潤性乳癌

- DCIS成分を有する浸潤性乳癌について、DCISの進展にかかわりなく、「no ink on tumor」の断端陰性の定義は、浸潤癌の断端ガイドラインに基づくべきである。この設定では、主にこれらの病変の自然史、治療、および転帰がDCISより浸潤癌に類似しているため、DCISまたは浸潤癌細胞のいずれに対しても「no ink on tumor」が推奨される。患者との話し合いを踏まえ、再切除を行う方がよいのではないかと思われる特異的な例では、臨床的判断を適用すべきである。
- APBIを受ける患者では、局所再発に関するデータが比較的限られているため、これらの断端の推奨を直接適用することはできない[2]。さらに、ケースバイケースで個々の患者毎に臨床的判断を行うべきであり、術後にマンモグラフィを用いて石灰化の残存を特定するとともに、断端近くの病変の定量的進展、広範な乳管内成分（EIC）の存在、若年、複数の断端近接などの臨床病理学的因子を特定することで、IBTRのリスクが高く、それにより再切除が有益な可能性のある患者の選択に役立てる。
- 浸潤性乳癌の患者では、BCS後にEICが存在せず顕微鏡的に断端が部分的陽性の場合[3]、腫瘍床に対する比較的高線量のブースト照射を考慮すべきである。再発リスクの高い患者では、腫瘍床へのブースト照射が推奨される。標準的な線量は10～16Gyで、1回2Gyの分割照射とする。

2 Morrow M, Van Zee KJ, Solin LJ, et al.Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ.J Clin Oncol 2016;34:4040-4046.

3 EICとは、腫瘍の体積の25%以上が非浸潤巣であり、非浸潤巣が浸潤巣を越えて周囲の正常な乳腺実質に進展している浸潤性乳管癌と定義される。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

放射線療法を要する乳房温存療法に関する特別な考慮点

放射線療法を要する乳房温存療法の禁忌は以下の通りである。

絶対的
- 妊娠中の放射線療法
- びまん性の疑いのある、または悪性の様相を呈している微小石灰化
- 乳房組織の単一領域または区域の局所切開による範囲に含めることができず、断端陰性と、満足できる整容性が達成できない広範な病変
- 広汎な病理学的断端陽性[1]
- ATM遺伝子変異がホモ接合体（両アレル不活化）（カテゴリー2B）

相対的
- 胸壁または乳房に対する放射線療法歴：処方線量および体積を把握することが重要である。
- 皮膚に波及した活動性の膠原病（特に強皮症や全身性エリテマトーデス）
- 5cm超の腫瘍（カテゴリー2B）
- 病理学的に断端陽性[1]
- 乳癌に対する遺伝学的素因が既知または疑われる女性：
  - 乳房温存療法では、同側乳房における再発または対側乳房における乳癌発症のリスクが増大する恐れがある。
  - リスク低減のための予防的両側乳房全切除術を考慮できる。
    （NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照）。
  - リ・フラウメニ症候群の可能性がある（カテゴリー2B）。

[1] DCISおよび浸潤性乳癌に対する断端状態による推奨（BINV-F）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術後乳房再建の原則

- 乳房再建は、乳癌の外科的治療を受けているすべての女性に対する選択肢になると考えられる。乳癌治療を受けているすべての女性に、個々の臨床状況に適応する乳房再建選択肢についての教育を行うべきである。ただし、乳房再建が乳癌の適切な外科的管理や乳癌の適切な外科的治療の対象範囲を妨げる要因となってはならない。形成外科医とのコンサルテーションおよび外科的治療の調整は妥当な時間枠のなかで進めるべきである。乳房再建プロセスは、乳癌の適切な外科的治療のタイミングまたは範囲を左右するものであってはならない。乳房再建が利用できることまたは実行できることによって、適切な外科的介入が遅延または拒否されてはならない。

- 乳房部分切除術によって考えられる美容上の結果を手術前に評価しておくべきである。切除自体が美容上受け入れられない結果を予想させる状況では、乳房再建に対する形成外科の技術を用いることで乳房温存手術の選択肢を広げることが可能である。それら技術を適用することにより、乳房の変形を最小限にとどめられると同時に、乳房全切除術を行う必要性が減り、再切除のための二次手術の実施も減少する可能性がある。切除断端陽性の可能性および二次手術が必要になるかもしれないことを患者に伝えておくべきであり、二次手術では、再切除としての部分切除などが行われ、乳頭の喪失を伴うまたは伴わない乳房全切除術が必要になる可能性もある。形成外科手術では、長期的な非対称性を最小限に抑えるため、健康な対側乳房に対する手術を組み合わせることもある。

- 乳房全切除術の場合、乳房再建の可能性を話し合い、再建選択肢についての術前評価を考えるべきである。乳房全切除術後の乳房再建を以下に示す。
  - 乳房インプラントを組み込んだ処置（例：組織拡張器挿入後インプラント挿入、即時インプラント挿入など）。
  - 自家組織移植を組み込んだ処置（例：有茎式腹直筋皮弁、脂肪移植、腹部、背部、殿部および大腿に由来する様々なマイクロサージャリー皮弁など）。
  - 乳房インプラントおよび自家組織移植を組み込んだ処置（例：広背筋皮弁など）。
- 乳房全切除術後の乳房再建は、乳房全切除術と同時に（「一次的」）または癌の治療が終了した後の時点で（「二次的」）開始される。多くの場合、乳房再建には以下のような段階を2つ以上必要とする段階的アプローチが取られる。
  - 対称性を向上させるための対側乳房への手術
  - 乳房やドナー部位の修正手術
  - 乳頭と乳輪の再建および入れ墨による着色

- どのような乳房全切除術でもそうであるが、皮膚温存乳房全切除術は、おそらく通常の乳房全切除術と同等に癌の局所再発リスクが存在することが示唆されている。皮膚温存乳房全切除術は、経験を積んだ乳房手術チームが協調して集学的に行い、患者の選択を適切に行うとともに術後療法との関係から最適な乳房再建手順を決定し、適切な切除断端状態を達成しなければならない。皮膚温存乳房全切除術を行った場合でも、標準的な乳房全切除術と同じ選択基準に従った乳房全切除術後放射線療法を適用しなければならない。

- 炎症性乳癌に対する乳房全切除術の場合、再発リスクが高いこと、乳癌の悪性度が高いこと、そのため局所制御を行うために、滞りなく、迅速に術後放射線療法に移る必要があることから、一次的再建は禁忌である。炎症性乳癌における皮膚温存乳房全切除術の安全性は実証されていないことから、乳房全切除術時またはあらかじめ炎症の及んでいる皮膚を切除する必要がある。そのため、この場合に一次再建を行う利益はない。

続く

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術後乳房再建の原則

- 一般に、癌治療のための皮膚温存乳房全切除術では乳頭乳輪の温存が断念される。しかしながら、経験を積んだ集学的チームによって慎重に選択された癌患者においては、乳頭温存手術も選択肢の1つとなりうる。後ろ向きデータからは、乳癌治療に対する乳頭温存手術の採用が支持されており、乳房体積が小さいか中程度で、下垂がごく軽度から中程度までの（術前の乳頭位置が受け入れられる）患者では、早期および局所進行浸潤癌および/またはDCISにおける乳頭浸潤率が低く、局所再発率が同程度であり、合併症発生率が低いと報告されている。パジェット病を含む乳頭浸潤の術前臨床所見、悪性腫瘍に伴う乳頭分泌、および/または乳頭や乳輪下組織の悪性腫瘍浸潤を示唆する画像所見がある場合は、乳頭温存は禁忌となる。乳頭断端の評価が不可欠であり、切除検体の乳頭断端は明確に特定すべきである。

- 放射線療法による治療歴がある患者では再建を行ってもよい（乳房全切除術と放射線療法の後では二次再建、乳房温存後に乳房全切除術を受ける患者では一次再建）。乳房全切除術と放射線療法の後に二次再建を受ける患者では、自家組織再建が望ましい。この状況での組織拡張器/インプラントベースの再建では、被膜拘縮、位置偏位、整容性の低下、インプラントの露出、および再建失敗のリスクが著しく高まる可能性がある。

- 乳頭温存療法後に救済乳房全切除術を受ける患者でのインプラントベースの再建は、自家組織再建より合併症発生率が高くなるが、術前因子と術中の考慮点に基づき適切に選択された患者では考慮してもよい。

- 非炎症性の局所進行乳癌は、一次再建の絶対禁忌ではないが、再建アプローチとは無関係に乳房全切除術後の放射線療法を行うべきである。
  - 乳房全切除術後放射線療法が必要で、自家組織再建が予定されている場合、再建を放射線療法が終了するまで延期することも、乳房全切除術時に再建を開始し、組織拡張器を挿入してから自家組織再建を行うことも可能である。経験豊富な乳癌チームでは、一次組織再建後に放射線療法を行うプロトコルが採用されているが、再建時の整容性の損失が報告されていることから、一般的に、自家組織移植前に放射線療法を行うことが推奨される（カテゴリー2B）。
  - 放射線療法を必要とする患者でインプラント法による再建が予定されている場合、一次組織拡張器挿入後にインプラントを挿入する段階的アプローチが推奨される。放射線療法前または放射線療法終了後に、組織拡張器を永久的インプラントと交換する手術を行うことができる。術前および術中の考慮点に基づき適切に選択された患者では、術後放射線療法が必要な患者における一次インプラント挿入（direct-to-implant）による再建を考慮してよい。

- どのような乳房再建方法を選択するかは、癌の治療状態の評価、体型、肥満、喫煙歴、併存疾患および患者の意向に基づいて決定される。喫煙と肥満は、インプラントか自家組織かにかかわらず、すべてのタイプの乳房再建で合併症の発生リスクを高める。したがって、喫煙と肥満は、乳房再建に対する相対的禁忌であると考えられ、喫煙者や肥満症患者では創傷治癒が遅れたり、あるいは皮弁による乳房再建が部分的または完全に失敗したりする可能性が高いことを患者に告知するべきである。

- 乳癌治療の終了後に整容性に満足しない女性には、形成外科の受診を勧めるべきである。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

放射線療法の原則

個々の照射の最適化

放射線療法の計画と実施を個別化することが重要である。標的体積および周囲のリスク臓器をコンツーリングするために、CT治療計画が推奨される。線量分布を均一にし、正常組織への照射を抑えることは、ウエッジのようなコンペンセータ、セグメントを用いたフォワードプラニング、および強度変調放射線療法（intensity-modulated radiation therapy：IMRT）を使用することで達成できる。

深吸気呼吸停止を含む呼吸制御技術や腹臥位を用いて、近接する正常組織（特に心臓および肺）への線量をさらに減らすことが可能である。乳房温存療法でのブースト照射は、正面（en face）からの電子線、光子線または小線源治療を用いて実施する。胸壁術後部へのブーストが必要な場合は、典型的には電子線または光子線が使用される。

日々のセットアップの再現性確認は、週1回の画像検査で実施する。特定の状況では、さらに頻繁な画像照合が適切な場合がある。毎日の画像照合のルーチン使用は推奨されない。

全乳房照射

標的の定義は全乳房組織である。全乳房への照射線量は、45～50.4Gy/25～28分割または40～42.5Gy/15～16分割とする（寡分割が望ましい）。いずれの照射線量でも、週5日間の照射とする。再発リスクの高い患者では、腫瘍床へのブースト照射が推奨される。標準的なブースト線量は、10～16Gy/4～8分割である。

胸壁照射（乳房再建を含む）

照射標的は、同側胸壁、乳房切除創、および必要時にはドレーン部分である。患者が乳房再建を受けているかどうかにより、光子線および/または電子線を用いる。肺および心臓の体積を同定し、これら臓器の被曝を最小限にするために、CT治療計画が推奨される。照射線量は、胸壁への45～50.4Gy/25～28分割照射±ブースト照射を含め総線量約60Gy/1.8～2Gyである。いずれの照射線量でも、週5日間の照射とする。皮膚への照射線量が適切になるように、ボーラスの使用を特に考慮すべきである。。

領域リンパ節照射

標的の輪郭描出は、CT治療計画により最適に達成される。鎖骨周辺および腋窩リンパ節については、患者の解剖学的構造により処方する深さが異なる。内胸リンパ節の同定には、リンパ節の位置の代わりに内胸動脈および静脈が用いられる（計画画像ではリンパ節自体が通常見えないため）。乳房全切除術後の放射線療法を検討したランダム化試験および最近の試験結果に基づき、領域リンパ節に照射する場合は内胸リンパ節への放射線照射を積極的に検討すべきである。内胸リンパ節領域への照射時には、正常組織（特に心臓および肺）への線量および遵守すべき線量制約を評価するために、CT治療計画を用いるべきである。照射線量は、領域リンパ節領域に対し46～50Gy/23～25分割である。いずれの照射線量でも、週5日間の照射とする。

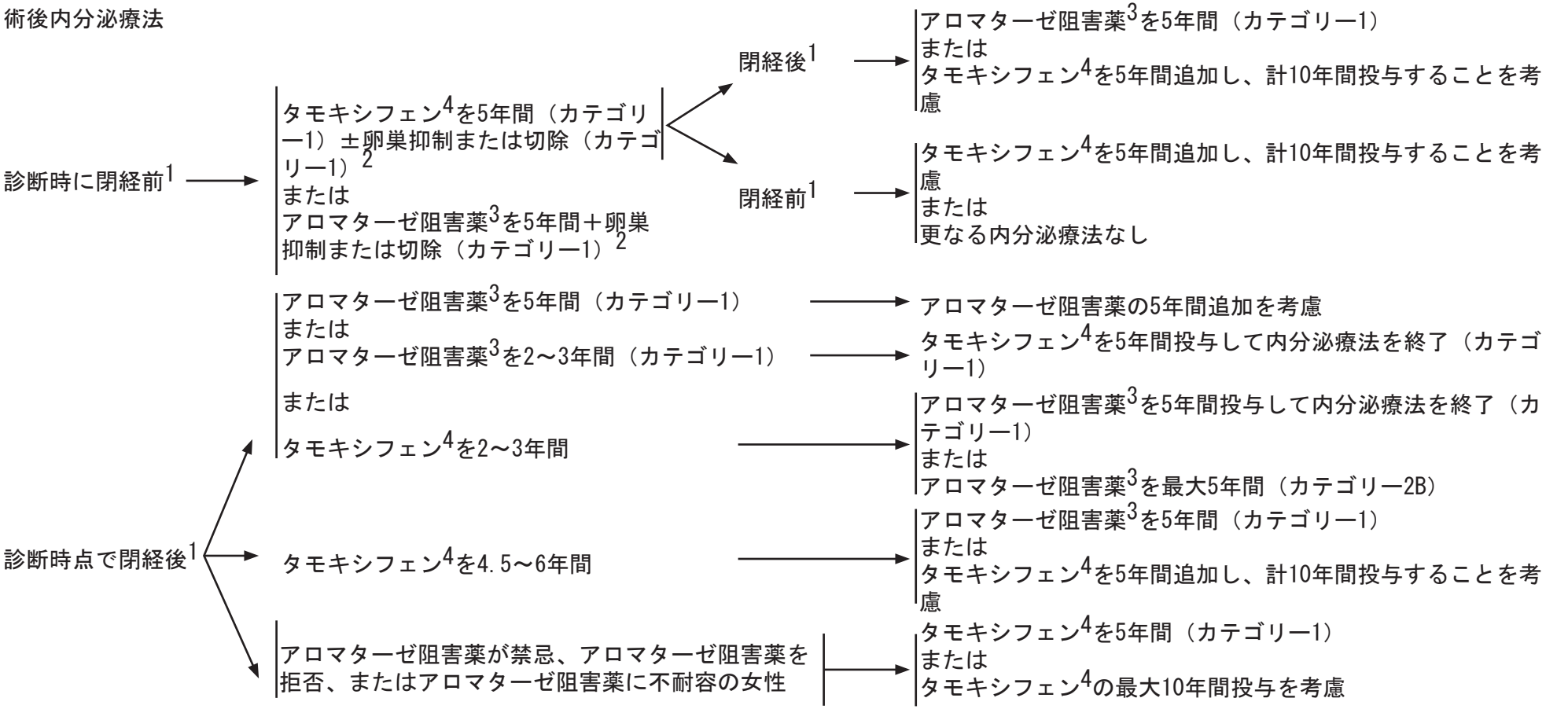
加速乳房部分照射法（accelerated partial breast irradiation：APBI）

APBIの予備研究から、一部の早期乳癌患者における局所制御率は標準分割全乳房照射を受けた患者と同等であることが示唆される。しかし、APBIによる整容性は標準分割全乳房照射と比べて劣ることが最近のいくつかの研究で示されている。追跡期間が短く、研究は現在も進行中である。患者の臨床試験への参加が推奨される。当NCCN委員会は、ASTROのAPBIガイドラインの2016年改訂版を受け入れており、この版では現在以下のいずれかに該当する患者をAPBIに「適している（suitable）」と定義している。1）50 歳以上の浸潤性乳管癌で、大きさが2cm以下（T1）、断端が2mm以上の陰 性、LVIなし、ER陽性、BRCA陰性；2）低/中間核異型度、検診でみつかったDCISで、大きさが2.5cm以下、断端が3mm以上陰性。腫瘍床への小線源による34Gy/10回1日2回照射または光子線体外照射による38.5Gy/10回1日2回照射が典型的には用いられる。他の分割法も現在検討されている。

術前薬物療法

術前薬物療法を受けた患者における放射線療法の適応および照射範囲は、治療前の臨床病期、病理学的病期の最大病期、および腫瘍の特徴に基づいて決定すべきである。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



1 閉経の定義（BINV-M）を参照のこと。

2 卵巣抑制療法に関連するリスクとベネフィットについてバランスのとれた考察が不可欠である。再発リスクが高い（すなわち、若年、high-gradeの腫瘍、リンパ節浸潤に該当する）閉経前女性では、臨床試験SOFTおよびTEXTの結果（Pagani, NEJM 2014, Prudence, NEJM 2014）に基づいて、アロマターゼ阻害薬またはタモキシフェン5年間と卵巣抑制療法を考慮すべきである。生存データはまだ得られていない。

3 当委員会は、術前または術後療法のランダム化試験において、3つの選択的アロマターゼ阻害薬（すなわち、アナストロゾール、レトロゾール、エキセメスタン）は同程度の抗腫瘍効果と同様の毒性プロファイルを示したと考えている。術後療法におけるアロマターゼ阻害薬の至適投与期間は不明である。

4 フルオキセチンおよびパロキセチンなどの一部SSRIは、タモキシフェンの活性代謝物であるエンドキシフェンおよび4-OHタモキシフェンの形成を抑制し、その有効性を変化させると考えられる。これらの薬物とタモキシフェンとの併用では、慎重投与が勧められる。ただし、シタロプラムとベンラファキシンはタモキシフェンの代謝にほとんど影響しないようである。現段階で、これまでのデータに基づき、当委員会は、タモキシフェン療法を検討している女性への*CYP2D6*遺伝子検査に反対する。強力な*CYP2D6*阻害剤の併用では、慎重投与が必要である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前/術後療法のレジメン[1,2,3,4,5]

HER2陰性[6]

・ 望ましいレジメン：
- Dose-dense（投与間隔短縮）AC（ドキソルビシン/シクロホスファミド）に続いてパクリタキセルの隔週投与[7]
- Dose-dense（投与間隔短縮）AC（ドキソルビシン/シクロホスファミド）に続いてパクリタキセルの週1回投与[7]
- TC（ドセタキセル/シクロホスファミド）

・ 特定の状況で有用：
- Dose-dense（投与間隔短縮）AC（ドキソルビシン/シクロホスファミド）
- AC（ドキソルビシン/シクロホスファミド）を3週間毎（カテゴリー2B）
- CMF（シクロホスファミド/メトトレキサート/フルオロウラシル）
- ACに続いてパクリタキセルを週1回

・ その他の推奨レジメン：
- ACに続いてドセタキセルを3週間毎
- EC（エピルビシン/シクロホスファミド）
- TAC（ドセタキセル/ドキソルビシン/シクロホスファミド）

HER2陽性

・ 望ましいレジメン：
- ACに続いてT＋トラスツズマブ[8]（ドキソルビシン/シクロホスファミドに続いてパクリタキセル＋トラスツズマブ、各種スケジュールにて）
- ACに続いてT＋トラスツズマブ＋ペルツズマブ[8]（ドキソルビシン/シクロホスファミドに続いてパクリタキセル＋トラスツズマブ＋ペルツズマブ）
- パクリタキセル＋トラスツズマブ[9]
- TCH（ドセタキセル/カルボプラチン/トラスツズマブ）
- TCH（ドセタキセル/カルボプラチン/トラスツズマブ）＋ペルツズマブ

・ 特定の状況で有用：
- ドセタキセル＋シクロホスファミド＋トラスツズマブ

・ その他の推奨レジメン：
- ACに続いてドセタキセル＋トラスツズマブ[8]（ドキソルビシン/シクロホスファミドに続いてドセタキセル＋トラスツズマブ）
- ACに続いてドセタキセル＋トラスツズマブ＋ペルツズマブ[8]（ドキソルビシン/シクロホスファミドに続いてドセタキセル＋トラスツズマブ＋ペルツズマブ）

1 HER2陽性腫瘍の患者では、アントラサイクリン系薬剤中心の化学療法の方がアントラサイクリン系薬剤以外を中心にした治療法よりも優れていることが、後向きのエビデンスによって示唆されている。
2 アントラサイクリン系薬剤中心の化学療法にタキサン系薬剤を追加すると予後が向上することが、ランダム化臨床試験によって実証されている。
3 CMFは放射線療法と同時に投与してもよいし、あるいはCMFを先に投与してもよい。その他の化学療法はすべて、放射線療法の前に投与するべきである。
4 術後療法としての化学療法と内分泌療法は、化学療法に続いて内分泌療法という順序で逐次的に施行すべきである。
5 医学的に必要であれば（すなわち過敏症反応のために）、パクリタキセルまたはドセタキセルに代わりにナブパクリタキセルを使用してもよい。週1回のパクリタキセルまたはドセタキセルの代用にする場合、ナブパクリタキセル週1回投与の用量は125mg/m^{2}を超えないようにすべきである。
6 HER2陰性乳癌に対してリストされたレジメンは、術後療法として使用する場合、すべてカテゴリー1である（適応がある場合を除く）。
7 パクリタキセルとその後のDose-dense（投与間隔短縮）ACへの投与順序の変更が受け入れられる。
8 トラスツズマブのアントラサイクリン系薬剤との併用については、重大な心毒性との関連が認められる。トラスツズマブおよびペルツズマブとアントラサイクリン系薬剤との併用は避けるべきである
9 低リスクかつT1, N0, M0のHER2陽性乳癌患者（特に、併存疾患のために他の標準的な術後療法レジメンに不適格とされた患者）には、パクリタキセル＋トラスツズマブを考慮してもよい。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前/術後療法のレジメン

HER2陰性
望ましいレジメンの投与スケジュール：

- Dose-dense（投与間隔短縮）ACに続いてパクリタキセル[1]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 14日サイクルで4サイクル[a]
    - ◊ 続いて：
  - パクリタキセル175mg/m²を1日目に3時間の点滴静注
    - ◊ 14日サイクルで4サイクル[a]

- Dose-dense（投与間隔短縮）ACに続いてパクリタキセルを週1回[1]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 14日サイクルで4サイクル[a]
    - ◊ 続いて：
  - パクリタキセル80mg/m²を1時間の点滴静注で週1回、12週間

- TC[2]
  - ドセタキセル75mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル[a]

HER2陰性
特定の状況で有用なレジメンの投与スケジュール：

- Dose-dense（投与間隔短縮）AC[1]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 14日サイクルで4サイクル[a]

- AC[3]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル

- CMF化学療法[4]
  - シクロホスファミド100mg/m²を1～14日目に服用
  - メトトレキサート40mg/m²を1および8日目に静注
  - フルオロウラシル600mg/m²を1および8日目に静注
    - ◊ 28日サイクルで6サイクル

- ACに続いてパクリタキセルを週1回[5]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル
    - ◊ 続いて
  - パクリタキセル80mg/m²を1時間の点滴静注で週1回、12週間

HER2陰性
その他の推奨レジメンの投与スケジュール：

- ACに続いてドセタキセルによる化学療法[6]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル
    - ◊ 続いて：
  - ドセタキセル100mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル

- EC化学療法[7]
  - エピルビシン100mg/m²を1日目に静注
  - シクロホスファミド830mg/m²を1日目に静注
    - ◊ 21日サイクルで8サイクル

- TAC化学療法[8]
  - ドセタキセル75mg/m²を1日目に静注
  - ドキソルビシン50mg/m²を1日目に静注
  - シクロホスファミド500mg/m²を1日目に静注
    - ◊ 21日サイクルで6サイクル[a]

[a] 全サイクルで骨髄増殖因子製剤を併用する；NCCN骨髄増殖因子ガイドラインを参照のこと。

抗癌剤の選択、用量設定および投与やそれに付随する毒性の管理は複雑である。予想される副作用や患者の個人差、前治療、併存疾患のために、薬剤の用量およびスケジュールの変更と支持療法の開始がしばしば必要になる。したがって、抗癌剤の最適な投与のためには、癌患者における抗癌剤の使用とそれに付随する副作用の管理の経験が豊富な医療チームが必要である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前/術後療法のレジメン

HER2陽性

望ましいレジメンの投与スケジュール：

- ACに続いてT＋トラスツズマブ[9]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル
    - ◊ 続いて：
  - パクリタキセル80mg/m²の1時間の点滴静注を週1回で12週間
    - ◊ ＋
  - パクリタキセルの初回投与時にトラスツズマブ4mg/kgを静注
    - ◊ 続いて：
  - トラスツズマブ2mg/kgの静注を週1回で1年間の治療を完遂。あるいは、パクリタキセル完了後にトラスツズマブ6mg/kgの静注を21日間隔で1年間の治療を完遂[b]

- ACに続いてT＋トラスツズマブ＋ペルツズマブ
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクルで4サイクル
    - ◊ 続いて：
  - ペルツズマブ840mgを1日目に静注、続いて420mgを静注
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを静注
  - パクリタキセル80mg/m²を1、8および15日目に静注
    - ◊ 21日サイクルで4サイクル
    - ◊ 続いて：
  - トラスツズマブ6mg/kgを1日目に静注
  - ペルツズマブ420mgを1日目に静注
    - ◊ 21日サイクルで1年間の治療を完遂[b]

- Dose-dense（投与間隔短縮）ACに続いてパクリタキセル＋トラスツズマブ[10]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 14日サイクルで4サイクル
    - ◊ 続いて：
  - パクリタキセル175mg/m²を1日目に3時間の点滴静注
    - ◊ 14日サイクルで4サイクル*
    - ◊ ＋
  - パクリタキセルの初回投与時にトラスツズマブ4mg/kgを静注
    - ◊ 続いて：
  - トラスツズマブ2mg/kgの静注を週1回で1年間の治療を完遂。あるいは、パクリタキセル完了後にトラスツズマブ6mg/kgの静注を21日間隔で1年間の治療を完遂[a, b]

- パクリタキセル＋トラスツズマブ[11]
  - パクリタキセル80mg/m²の静注を週1回で12週間
    - ◊ ＋
  - パクリタキセルの初回投与時にトラスツズマブ4mg/kgを静注
    - ◊ 続いて：
  - トラスツズマブ2mg/kgの静注を週1回で1年間の治療を完遂。あるいは、パクリタキセル完了後にトラスツズマブ6mg/kgの静注を21日間隔で1年間の治療を完遂

- TCH[12]
  - ドセタキセル75mg/m²を1日目に静注
  - カルボプラチンをAUC 6で1日目に静注
    - ◊ 21日サイクルで6サイクル
    - ◊ ＋
  - トラスツズマブ4mg/kgを1週目に静注
    - ◊ 続いて：
  - トラスツズマブ2mg/kgを17週間静注
    - ◊ 続いて：
  - トラスツズマブ6mg/kgを静注
    - ◊ 21日サイクルで1年間の治療を完遂[b]

または

  - トラスツズマブ8mg/kgを1週目に静注
    - ◊ 続いて：

- トラスツズマブ6mg/kgを静注
  - ◊ 21日サイクルで1年間の治療を完遂[b]

- TCH＋ペルツズマブ[13]
  - ドセタキセル75mg/m²を1日目に静注
  - カルボプラチンをAUC 6で1日目に静注
    - ◊ 21日サイクルで6サイクル
    - ◊ ＋
  - トラスツズマブ8mg/kgを1日目に静注
  - ペルツズマブ840mgを1日目に静注
    - ◊ 続いて：
  - トラスツズマブ6mg/kgを1日目に静注
  - ペルツズマブ420 mgを1日目に静注
    - ◊ 21日サイクルで1年間の治療を完遂[b]

[a] 全サイクルで骨髄増殖因子製剤を併用する；NCCN骨髄増殖因子ガイドラインを参照のこと。

[b] 治療前および治療中に左室駆出率（LVEF）を評価する。トラスツズマブによる術後治療中のLVEFの至適測定頻度は不明である。FDAの添付文書では、トラスツズマブの開始前および治療中に3ヵ月間隔でのLVEFの測定が推奨されている。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前/術後療法のレジメン

HER2陽性
特定の状況で有用なレジメンの投与スケジュール：

・ドセタキセル/シクロホスファミド＋トラスツズマブ[14]
- ドセタキセル75mg/m²を1日目に静注
- シクロホスファミド600mg/m²を1日目に静注
  - ◊ 21日サイクルで4サイクル
  - ◊ ＋
- トラスツズマブ4mg/kgを1週目に静注
  - ◊ 続いて
- トラスツズマブ2mg/kgを週1回で11週間静注
  - ◊ 続いて
- トラスツズマブ6mg/kgを静注
  - ◊ 21日サイクルで1年間のトラスツズマブ治療を完遂[b]

または
- トラスツズマブ8 mg/kgを1週目に静注
  - ◊ 続いて：
- トラスツズマブ6mg/kgを21日間隔で静注し、1年間のトラスツズマブ治療を完遂[b]

HER2陽性
その他の推奨レジメンの投与スケジュール：

・ACに続いてドセタキセル＋トラスツズマブ[11]
- ドキソルビシン60mg/m²を1日目に静注
- シクロホスファミド600mg/m²を1日目に静注
  - ◊ 21日サイクルで4サイクル
  - ◊ 続いて：
- ドセタキセル100 mg/m²を1日目に静注
  - ◊ 21日サイクルで4サイクル
  - ◊ ＋
- トラスツズマブ4mg/kgを1週目に静注
  - ◊ 続いて：
- トラスツズマブ2mg/kgを週1回で11週間静注
  - ◊ 続いて：
- トラスツズマブ6mg/kgを静注
  - ◊ 21日サイクルで1年間のトラスツズマブ治療を完遂[b]

・ACに続いてドセタキセル＋トラスツズマブ＋ペルツズマブ
- ドキソルビシン60mg/m²を1日目に静注
- シクロホスファミド600mg/m²を1日目に静注
  - ◊ 21日サイクルで4サイクル
  - ◊ 続いて：
- ペルツズマブ840mgを1日目に静注、続いて420mgを静注
- トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを静注
- ドセタキセル75～100mg/m²を1日目に静注
  - ◊ 21日サイクルで4サイクル
  - ◊ 続いて：
- トラスツズマブ6mg/kgを静注
- ペルツズマブ420 mgを1日目に静注
  - ◊ 21日サイクルで1年間の治療を完遂[b]

[b] 治療前および治療中に左室駆出率（LVEF）を評価する。トラスツズマブによる術後治療中のLVEFの至適測定頻度は不明である。FDAの添付文書では、トラスツズマブの開始前および治療中に3ヵ月間隔でのLVEFの測定が推奨されている。

抗癌剤の選択、用量設定および投与や付随する毒性の管理は複雑である。予想される副作用や患者の個人差、前治療、併存疾患のために、薬剤の用量およびスケジュールの変更と支持療法の開始がしばしば必要になる。したがって、抗癌剤の最適な投与のためには、癌患者における抗癌剤の使用と付随する副作用の管理について豊富な経験を有する医療チームが必要である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前/術後療法のレジメンに関する参考文献

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臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

術前薬物療法の原則

- 化学療法のランダム化臨床試験により、術前に術後と同じ治療を行った場合に同程度の長期成績が得られることが実証されている[1]。
- 術前薬物療法では、外科的に手術不能な腫瘍を手術可能にすることができるとともに、手術可能な乳癌患者にも有益となる可能性がある。重要な点として、術前薬物療法を行うことで、乳房温存療法に適格となる可能性が高まり、腋窩手術の範囲が最小限に抑えられるとともに、個々の患者で全身療法による臨床的および病理学的奏効が得られる可能性がある。
- 術前薬物療法に対する病理学的完全奏効（pCR）に伴い、極めて良好な無病生存および全生存期間が得られ、特にすべての治療を術前に行う状況で顕著である。病理学的奏効と長期成績の相関は、トリプルネガティブ乳癌（TNBC）で最も強く、HER2陽性乳癌でやや劣り、ER陽性乳癌で最も弱い[2,3]。
- 術前療法としては、いくつかの化学療法レジメンが有効である。一般に、術後療法として推奨されている化学療法は術前治療として考慮してもよい。術前/術後療法のレジメン（BINV-K）を参照のこと。
- ER陽性例には、併存疾患または低リスクのluminal型である場合には、術前内分泌療法単独を考慮してもよい。
- HER2陽性乳癌の患者には、9週間以上の術前療法としてトラスツズマブを含む術前化学療法を行うべきである。T2以上またはN1以上のHER2陽性早期乳癌患者では、術前にペルツズマブを含むレジメンを投与してもよい。術前/術後療法のレジメン（BINV-K）を参照
- 術前薬物療法を受けた患者では、術後薬物療法を受けた場合と比較して局所再発リスクが高いことが一部の研究で報告されている[4]。この局所再発リスクの増加は、術前治療を受けた患者において、最適ではない根治目的の局所療法が施行されたことが原因であるとされている。
- すべての患者が術前薬物療法の適切な候補となるわけではない。術前薬物療法の開始前のベースライン時の正確な臨床病期分類が極めて重要である。術前薬物療法：乳房および腋窩リンパ節診断（BINV-11）を参照
- 術前化学療法を選択した場合は、すべての治療を手術療法の前に実施すべきである。術前療法の実施中は、臨床的な評価により腫瘍の治療効果をルーチンで評価する必要がある。手術可能な乳癌患者で術前薬物療法中に進行がみられた場合は、代替の全身療法に切り替えるか、手術を施行する。術後薬物療法を受ける患者と同様な方法で、局所療法の原則を適用すべきである。

1 Rastogi P, Anderson SJ, Bear HD, et al.Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27.J Clin Oncol 2008 Feb 10;26(5):778-85.
2 von Minckwitz G, Untch M, Blohmer JU, et al.Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes.J Clin Oncol 2012 May 20;30(15):1796-804.
3 Cortazar P, Zhang L, Untch M, et al.Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis.Lancet 2014 Jul 12;384(9938):164-72.
4 Mauri D, Pavlidis N, Ioannidis JP.Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis.J Natl Cancer Inst 2005 Feb 2;97(3):188-94.

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臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

続く

術前薬物療法の原則

術前薬物療法で知られている有益性
- 乳房温存が容易となる
- 手術不能腫瘍が手術可能になる
- 治療への反応に基づき個々の患者レベルで重要な予後情報が得られ、特にHER2陽性のトリプルネガティブ乳癌患者で重要である
- 遺伝子検査が時間的に可能となる
- 乳房全切除術を選択した患者でも、乳房再建が計画できる時間が得られる

機会
- 腋窩リンパ節転移陽性が治療により陰性になれば、SLNB単独が可能になる
- 術前療法に対する反応がみられない場合や進行した場合に全身療法を変更する機会が得られる
- 奏効不良であれば、術後療法の追加が可能になるかもしれない
- 腋窩リンパ節の病変が消失すれば、放射線療法部分を小さくしたり、放射線療法を少なくしたりできる
- 新規治療法および予測バイオマーカーを検証する優れた研究基盤となる

注意
- 臨床病期が過大評価された場合、全身療法により過剰治療となる可能性がある
- 臨床病期が過小評価された場合、放射線療法により局所的に過小治療となる可能性がある
- 術前薬物療法中に病勢進行となる可能性がある

術前薬物療法の適応がある患者
- 手術不能乳癌の患者：
  - 炎症性乳癌
  - 巨大または癒合した腋窩リンパ節のN2
  - N3
  - T4
- 手術可能乳癌の患者：
  - 乳房温存を希望する患者で、乳房の大きさと比較して原発腫瘍が大きい
  - リンパ節転移陽性病変があるが、術前薬物療法によりリンパ節転移陰性となる可能性が高い

術前薬物療法の候補とならない患者
- 広範な非浸潤性癌で、浸潤癌範囲の確定が不十分な患者
- 腫瘍範囲の境界が曖昧な患者
- 腫瘍が触診不能または臨床的に評価できない患者

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

閉経の定義

乳癌の臨床試験は多様な閉経の定義を利用している。閉経は一般に月経の永久的な停止を指し、乳癌の管理でこの用語が用いられる場合は、卵巣によるエストロゲン合成の顕著かつ永久的な低下を意味する。閉経を判定する基準の妥当なものとして以下のものが挙げられる：

- 両側性卵巣摘出術の既往がある
- 年齢が60歳以上である
- 年齢が60歳未満であり、化学療法、タモキシフェン、トレミフェン、卵巣抑制を受けていないにもかかわらず12ヵ月以上にわたって無月経で、卵胞刺激ホルモン（FSH）とエストラジオールの測定値が閉経後の範囲にある
- タモキシフェンまたはトレミフェンを使用していて、かつ年齢が60歳未満である場合は、FSHと血漿エストラジオール濃度が閉経後の範囲にある

LHRH作動薬または拮抗薬の投与を受けている女性では閉経状況を判定することができない。術後化学療法開始時に閉経前であった女性では、化学療法後に無排卵/無月経となっても卵巣機能が健在であったり回復したりする可能性があるため、無月経が閉経状況の確実な指標とならない。このような治療誘発性無月経の女性で内分泌療法の一部としてアロマターゼ阻害薬の使用を考慮する場合は、閉経後状態を確保するために卵巣切除術やFSHおよび/またはエストラジオールの連続測定が必要である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

ERおよび/またはPR陽性の再発/IV期（M1）に対する全身療法

HER2陰性かつ閉経前
IV期（M1）の全身療法（BINV-20）を参照

HER2陰性かつ閉経後
望ましいレジメン：
- 非ステロイド系アロマターゼ阻害薬（アナストロゾール、レトロゾール）
- 選択的エストロゲン受容体ダウンレギュレーター（フルベストラント、カテゴリー1）[1]
- タモキシフェンまたはトレミフェン
- ステロイド系アロマターゼ不活化薬（エキセメスタン）
- パルボシクリブ＋アロマターゼ阻害薬（カテゴリー1）[2,3]
- パルボシクリブ＋フルベストラント（カテゴリー1）[2,4]
- Ribociclib＋アロマターゼ阻害薬（カテゴリー1）[2,3]
- Abemaciclib＋アロマターゼ阻害薬（カテゴリー1）[2,3]
- Abemaciclib＋フルベストラント（カテゴリー1）[2,5]
- エキセメスタン＋エベロリムス[2,6]
- フルベストラント＋エベロリムス
- タモキシフェン＋エベロリムス
- Ribociclib＋タモキシフェン（カテゴリー1）[2,7]

特定の状況で有用：
- 酢酸メゲストロール
- フルオキシメステロン
- エチニルエストラジオール
- Abemaciclib[2,8]

HER2陽性で閉経前
IV期（M1）の全身療法（BINV-22）を参照

HER2陽性で閉経後
- アロマターゼ阻害薬±トラスツズマブ
- アロマターゼ阻害薬±ラパチニブ
- アロマターゼ阻害薬±ラパチニブ＋トラスツズマブ
- フルベストラント±トラスツズマブ
- タモキシフェン±トラスツズマブ

1 転移巣に対する化学療法、生物製剤または内分泌療法による治療歴のないホルモン受容体陽性乳癌の女性を対象とした単一の研究（SO226）により、アナストロゾールにフルベストラントを追加することで無増悪期間が延長することが検証された。サブセット解析では、タモキシフェンによる術後療法を受けていない診断後10年以後の患者で最も有益となることが示唆された。同様のデザインを採用した2つの研究（FACTおよびSOFEA）では、アナストロゾールにフルベストラントを追加しても、無増悪期間の延長は認められなかった。

2 CDK4/6阻害薬による治療中に進行がみられた場合については、CDK4/6阻害薬を含む別のレジメンによる更なる治療の実施を裏付けるデータはない。同様に、エベロリムスを含むレジメンによる治療中に病勢がみられた場合についても、エベロリムスを含む別のレジメンによる更なる治療の実施を裏付けるデータもない。

3 閉経後のホルモン受容体陽性HER2陰性転移乳癌患者の一次治療選択肢としてCDK4/6阻害薬とアロマターゼ阻害薬（アナストロゾール、レトロゾールまたはエキセメスタン）との併用を考慮してもよい。

4 閉経後の女性またはLHRH作動薬による卵巣抑制を受けている閉経前女性で、以前の術後または転移内分泌療法中またはその後に進行が認められたホルモン受容体陽性HER2陰性転移乳癌患者が対象となる。

5 以前の内分泌療法で進行した場合に適応となる。

6 エキセメスタンとエベロリムスの併用を、BOLERO-2選択基準を満たした患者（12ヵ月以内または非ステロイド系アロマターゼ阻害薬の投与中に病勢進行を認める）に対して考慮することができる。

7 閉経前のホルモン受容体陽性HER2陰性転移乳癌患者の一次治療選択肢として卵巣抑制または卵巣切除を考慮してもよい。

8 転移の設定で以前の内分泌療法または化学療法で進行した場合に適応となる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）に対する化学療法レジメン[1]

HER2陰性 単剤[2]

望ましいレジメン：
- アントラサイクリン系薬剤
  - ドキソルビシン
  - リポソーム封入ドキソルビシン
- タキサン系薬剤
  - パクリタキセル
- 代謝拮抗薬
  - カペシタビン
  - ゲムシタビン
- 微小管阻害薬
  - ビノレルビン
  - エリブリン
- PARP阻害薬
  - オラパリブ（HER2陰性乳癌で生殖細胞系*BRCA1/2*変異を有する患者に対する選択肢）[3]

HER2陰性 併用レジメン[2]

望ましいレジメン：
- なし[2]

特定の状況で有用[2]：
- AC（ドキソルビシン/シクロホスファミド）
- EC（エピルビシン/シクロホスファミド）
- CMF（シクロホスファミド/メトトレキサート/フルオロウラシル）
- ドセタキセル/カペシタビン
- GT（ゲムシタビン/パクリタキセル）
- ゲムシタビン/カルボプラチン
- パクリタキセル/ベバシズマブ[4]

HER2陽性

望ましいレジメン：
- ペルツズマブ＋トラスツズマブ＋ドセタキセル（カテゴリー1）[5]
- ペルツズマブ＋トラスツズマブ＋パクリタキセル[5]

その他の推奨レジメン：
- トラスツズマブ エムタンシン（T-DM1）
- トラスツズマブ＋パクリタキセル[5]±カルボプラチン
- トラスツズマブ＋ドセタキセル[5]
- トラスツズマブ＋ビノレルビン[5]
- トラスツズマブ＋カペシタビン
- ラパチニブ＋カペシタビン
- トラスツズマブ＋ラパチニブ（細胞傷害性薬剤と併用しない）
- トラスツズマブ＋他の薬剤[5,6,7]

その他の推奨レジメン：

- シクロホスファミド
- カルボプラチン
- ドセタキセル
- アルブミン結合パクリタキセル
- シスプラチン
- エピルビシン
- Ixabepilone

1 医学的に必要であれば（すなわち過敏症反応のために）、パクリタキセルまたはドセタキセルに代わりにナブパクリタキセルを使用してもよい。週1回のパクリタキセルまたはドセタキセルの代用にする場合、ナブパクリタキセル週1回投与の用量は125mg/m^{2}を超えないようにすべきである。

2 単剤の連続使用が望ましいが、腫瘍量が多く、急速進行性で生命を脅かす内臓転移のある選択された患者では、併用化学療法が使用できる。

3 単剤療法に適格なHER2陰性例には、生殖細胞系BRCA 1/2変異の検査を強く考慮する。

4 転移乳癌のランダム化試験から、一部の一次または二次化学療法にベバシズマブを追加することによって、無増悪期間と奏効率がわずかに改善されるが、全生存期間は改善しないことが実証されている。無増悪期間に対する効果は、併用する細胞傷害性薬剤によって異なる場合があり、ベバシズマブを週1回のパクリタキセルと併用した場合に最も大きくなるとみられる。

5 過去に転移例としてペルツズマブの併用なしで化学療法＋トラスツズマブによる治療を受けた患者では、細胞傷害性薬剤（ビノレルビンやタキサン系薬剤など）の併用の有無にかかわらず、トラスツズマブとペルツズマブの両方を含む1ラインの治療を考慮してもよい。抗HER2療法のための理想的な逐次併用の投与戦略を確立するには、更なる研究が必要である。

6 トラスツズマブのアントラサイクリン系薬剤との併用については、重大な心毒性との関連が認められる。トラスツズマブおよびペルツズマブとアントラサイクリン系薬剤との併用は避けるべきである

7 トラスツズマブは、再発または転移乳癌に対する上記リストに記載された望ましい単剤およびその他の単剤を含むアントラサイクリン系薬剤以外のすべてと安全に併用できる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）に対する化学療法レジメン

HER2陰性、単剤
望ましいレジメンの投与スケジュール：

- アントラサイクリン系薬剤：
  - ドキソルビシン60～75mg/m²を1日目に静注
    - ◊ 21日サイクル[1]
  - ドキソルビシン20mg/m²を1日目から週1回静注[2]
  - リポソーム封入ドキソルビシン[3] 50mg/m²を1日目に静注
    - ◊ 28日サイクル

- タキサン系薬剤：
  - パクリタキセル175mg/m²を1日目に静注
    - ◊ 21日サイクル[4]
  - パクリタキセル80mg/m²を1日目から週1回静注[5]

- 代謝拮抗薬：
  - カペシタビン[6] 1000～1250mg/m²を1～14日目に1日2回服用
    - ◊ 21日サイクル
  - ゲムシタビン[7] 800～1200mg/m²を1、8および15日目に静注
    - ◊ 28日サイクル

- 微小管阻害薬：
  - ビノレルビン[8] 25mg/m²を1日目から週1回静注
  - エリブリン[9] 1.4mg/m²を1日目および8日目に静注
    - ◊ 21日サイクル

- PARP阻害薬：
  - オラパリブ[10]錠剤[a]：300mgを1日2回服用
    - ◊ 28日サイクル

HER2陰性、単剤
その他の推奨レジメンの投与スケジュール：

- シクロホスファミド[11] 50mgを1～21日目に連日服用
  - 28日サイクル

- カルボプラチン[12] AUC 6で1日目に静注
  - 21～28日サイクル

- ドセタキセル[13,14] 60～100mg/m²を1日目に静注
  - 21日サイクル

- ドセタキセル[15] 35mg/m²を週1回、6週間の静注に続いて2週間の休薬、これを反復

- アルブミン結合パクリタキセル[16,17] 100mg/m²または125mg/m²を1、8および15日目に静注
  - 28日サイクル

- アルブミン結合パクリタキセル[16] 260mg/m²を静注
  - 21日サイクル

- シスプラチン[18] 75mg/m²を1日目に静注
  - 21日サイクル

- エピルビシン[19] 60～90mg/m²を1日目に静注
  - 21日サイクル

- Ixabepilone [20] 40mg/m²を1日目に静注
  - 21日サイクル

HER2陰性、併用レジメン
特定の状況で有用なレジメンの投与スケジュール：

- AC[21]
  - ドキソルビシン60mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクル

- EC[22]
  - エピルビシン75mg/m²を1日目に静注
  - シクロホスファミド600mg/m²を1日目に静注
    - ◊ 21日サイクル

- CMF[23]
  - シクロホスファミド100mg/m²を1～14日目に服用
  - メトトレキサート40mg/m²を1および8日目に静注
  - フルオロウラシル600mg/m²を1および8日目に静注
    - ◊ 28日サイクル

- ドセタキセル/カペシタビン[24]
  - ドセタキセル75mg/m²を1日目に静注
  - カペシタビン950mg/m²を1～14日目に1日2回服用
    - ◊ 21日サイクル

- GT[25]
  - パクリタキセル175mg/m²を1日目に静注
  - ゲムシタビン1250mg/m²を1および8日目に静注（1日目のパクリタキセルの後）
    - ◊ 21日サイクル

- ゲムシタビン/カルボプラチン[26]
  - ゲムシタビン1000mg/m²を1および8日目に投与
  - カルボプラチンをAUC 2で1および8日目に静注
    - ◊ 21日サイクル

- パクリタキセル＋ベバシズマブ[27]
  - パクリタキセル90mg/m²を1、8および15日目に静注
  - ベバシズマブ10mg/kgを1および15日目に静注
    - ◊ 28日サイクル

[a] カプセル製剤も利用可能である。ただし、投与法およびバイオアベイラビリティの違いにより、同じmg数で錠剤をカプセル剤に置き換えてはならない。

抗癌剤の選択、用量設定および投与や付随する毒性の管理は複雑である。予想される副作用や患者の個人差、前治療、併存疾患のために、薬剤の用量およびスケジュールの変更と支持療法の開始がしばしば必要になる。したがって、抗癌剤の最適な投与のためには、癌患者における抗癌剤の使用と付随する副作用の管理について豊富な経験を有する医療チームが必要である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）に対する化学療法レジメン

HER2陽性
望ましいレジメンの投与スケジュール：

- ペルツズマブ＋トラスツズマブ＋ドセタキセル[28]
  - ペルツズマブ840mgを1日目に静注、続いて420mgを静注
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを静注
  - ドセタキセル75～100mg/m²を1日目に静注
    ◊ 21日サイクル

- ペルツズマブ＋トラスツズマブ＋パクリタキセル[29]
  - ペルツズマブ840mgを1日目に静注、続いて420mgを静注
    ◊ 21日サイクル
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]
  - パクリタキセル80mg/m²を1日目から週1回静注[29]
    または
  - パクリタキセル175mg/m²を1日目に投与
    ◊ 21日サイクル

HER2陽性
その他の推奨レジメンの投与スケジュール：

- トラスツズマブ エムタンシン（T-DM1）[31]
  - 3.6mg/kgを1日目に静注
    ◊ 21日サイクル

- パクリタキセル/カルボプラチン＋トラスツズマブ[32]
  - カルボプラチンをAUC 6で1日目に静注
  - パクリタキセル175mg/m²を1日目に静注
    ◊ 21日サイクル
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

- パクリタキセル/カルボプラチン＋トラスツズマブを週1回[33]
  - パクリタキセル80mg/m²を1、8および15日目に静注
  - カルボプラチンをAUC 2で1、8および15日目に静注
    ◊ 28日サイクル
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

- トラスツズマブ＋パクリタキセル
  - パクリタキセル175mg/m²を1日目から21日毎に静注[34]
    または
  - パクリタキセル80～90mg/m²を1日目から週1回静注[35]
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

- トラスツズマブ＋ドセタキセル
  - ドセタキセル80～100mg/m²を1日目から21日毎に静注[36]
    または
  - ドセタキセル35mg/m²を1、8および15日目（週1回）に静注[37]
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

抗癌剤の選択、用量設定および投与や付随する毒性の管理は複雑である。予想される副作用や患者の個人差、前治療、併存疾患のために、薬剤の用量およびスケジュールの変更と支持療法の開始がしばしば必要になる。したがって、抗癌剤の最適な投与のためには、癌患者における抗癌剤の使用と付随する副作用の管理について豊富な経験を有する医療チームが必要である。

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臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発/IV期（M1）に対する化学療法レジメン

HER2陽性

その他の推奨レジメンの投与スケジュール：

- トラスツズマブ＋ビノレルビン[38,39]
  - ビノレルビン25mg/m²を1日目から週1回静注
    または
  - ビノレルビン30～35mg/m²を1日目および8日目に静注
    ◊ 21日サイクル
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

- トラスツズマブ＋カペシタビン[40]
  - カペシタビン1000～1250mg/m²を1～14日目に1日2回服用、21日サイクル
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注[34,41]
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

- ラパチニブ＋カペシタビン[42]
  - ラパチニブ1250mgを1～21日目に1日1回服用
  - カペシタビン1000 mg/m²を1～14日目に1日2回服用
    ◊ 21日サイクル

- トラスツズマブ＋カペシタビン[43]
  - カペシタビン1000～1250mg/m²を1～14日目に1日2回服用
    ◊ 21日サイクル
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注[34,41]
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

- トラスツズマブ＋ラパチニブ[44]
  - ラパチニブ1000mgを1日1回服用
  - トラスツズマブ4mg/kgを1日目に静注、続いて2mg/kgを週1回静注
    または
  - トラスツズマブ8mg/kgを1日目に静注、続いて6mg/kgを21日毎に静注[30]

抗癌剤の選択、用量設定および投与や付随する毒性の管理は複雑である。予想される副作用や患者の個人差、前治療、併存疾患のために、薬剤の用量およびスケジュールの変更と支持療法の開始がしばしば必要になる。したがって、抗癌剤の最適な投与のためには、癌患者における抗癌剤の使用と付随する副作用の管理について豊富な経験を有する医療チームが必要である。

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臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

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続く

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再発/IV期（M1）に対する化学療法レジメン（参考文献）

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遠隔転移のモニタリングの原則

転移乳癌の治療中に患者の症状および癌の組織量をモニタリングすることは、治療が有益であるか否か、また無効な治療に起因する毒性が患者に発現していないことを明らかにするために重要である。

モニタリングの内容：
モニタリングでは、症状、身体診察、ルーチンの臨床検査、画像検査、必要に応じて血中バイオマーカー測定を様々に組み合わせて定期的評価を行う。モニタリングの結果は、治療奏効/奏効継続、病勢安定、病状不確実または病勢進行に分類される。臨床医は、様々な情報を評価および比較し、乳癌がコントロールされているかどうか、治療による毒性は許容範囲内かどうかを判断しなければならない。この情報は相反する場合もある。

病勢進行の定義：
治療無効または適用された治療に対する耐性獲得のいずれが原因としても、病勢進行を立証するには、これらの因子1個以上による病勢進行を示す明確な証拠が求められる。病勢進行は、既知乳癌部位における乳癌の増大または増悪や、新たな部位への遠隔転移発生を示す証拠によって特定されると考えられる。

- 病勢進行に関する所見を以下に記す。
  - 疼痛または呼吸困難などの症状が増悪
  - 身体診察で、増悪または新規病変が認められる
  - 全身状態（PS）の低下
  - 説明のつかない体重減少
  - アルカリホスファターゼ、ALT、ASTまたはビリルビンの増加
  - 高カルシウム血症
  - 画像診断上、新規病変または既存病変のサイズ増大
  - 機能的画像検査（骨シンチグラフィ、PET/CTなど）における異常領域の新規出現
  - 腫瘍マーカー（CEA、CA15-3、CA27.29など）の上昇[1]

[1] 腫瘍マーカー（CEA、CA15-3、CA27.29など）の増加は腫瘍の進行に関係するが、治療が奏効している状況でもみられる場合がある。腫瘍マーカーの増加だけで、病勢進行が断言されることはほとんどない。骨病変の変化は、単純X線もしくは断面X線検査または骨シンチグラフィで評価し難い場合が多い。これらの理由から、骨優勢の遠隔転移の場合、患者の症状および血清中腫瘍マーカー測定の方が有用な場合がある。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

続く

遠隔転移のモニタリングの原則

奏効/安定/進行の客観的評価基準の使用

- 最も正確な病勢評価は、以前に異常を認めた検査を連続して、定期的に繰り返すことによって得られる場合が多い。一般的に、同じ評価方法を長く使用するべきである。例えば、胸部CTで検出された異常は、通常は再度胸部CTを行うことによってモニタリングする。
- 一連の検査において、臨床的に重要でない変動が生じることは多く、予測されたことである。したがって、奏効、安定および進行の評価には広く受け入れられている客観的な基準を採用することが推奨される。そのような基準としては、Response Evaluation Criteria In Solid Tumors（RECIST）ガイドライン（Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247）とWHO基準（Miller AB, Hoogstraten B, Staquet M, and Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207-214)がある。
- 機能的画像検査（例えば、放射性核種を用いる骨シンチグラフィやPETなど）は、反応評価に用いる際に特に課題が多い。骨シンチグラフィでは、奏効した場合に、スキャンでフレアまたは活性増強が認められる。特に新しい治療を開始後の初回フォローアップ骨シンチグラフィで、誤って病勢進行と解釈される可能性がある。PET画像検査は、病勢評価のための再現性や、再検証の欠如、広く認められている標準が存在しないため、課題が多い。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

続く

遠隔転移のモニタリングの原則

モニタリングの頻度

再検査の至適頻度は明確でなく、主に乳癌の臨床試験で用いられているモニタリング方法に基づく。モニタリングの頻度は、病勢進行を検出する必要と、無効な治療による不必要な毒性の回避、資源利用および費用を比較して決定しなければならない。下の表にガイダンスを示すが、病変の部位、疾患の生物学的特徴および治療レジメンに基づき、患者毎に調整する必要がある。遠隔転移の徴候や症状が新規に発現または増悪した患者については、前回検査からの時間に関係なく、病勢の再評価を行うべきである。

転移乳癌患者に対して提案される追跡間隔[2]

	新規治療開始前のベースライン	化学療法	内分泌療法	病勢進行が懸念される場合の病期再評価
症状評価	実施	各サイクル前	1～3ヵ月毎	実施
身体診察	実施	各サイクル前	1～3ヵ月毎	実施
全身状態（PS）	実施	各サイクル前	1～3ヵ月毎	実施
体重	実施	各サイクル前	1～3ヵ月毎	実施
肝機能、血算	実施	各サイクル前	1～3ヵ月毎	実施
胸部/腹部/骨盤の造影CT	実施	2～4サイクル毎	2～6ヵ月毎	実施
骨シンチグラフィ	実施	4サイクル毎	4～6ヵ月毎	実施
PET/CT	任意	任意	任意	任意
腫瘍マーカー	任意	任意	任意	任意

2 長期間の病勢安定を認める患者では、モニタリングの頻度を減らすことができる。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

葉状腫瘍

ガイドライン索引
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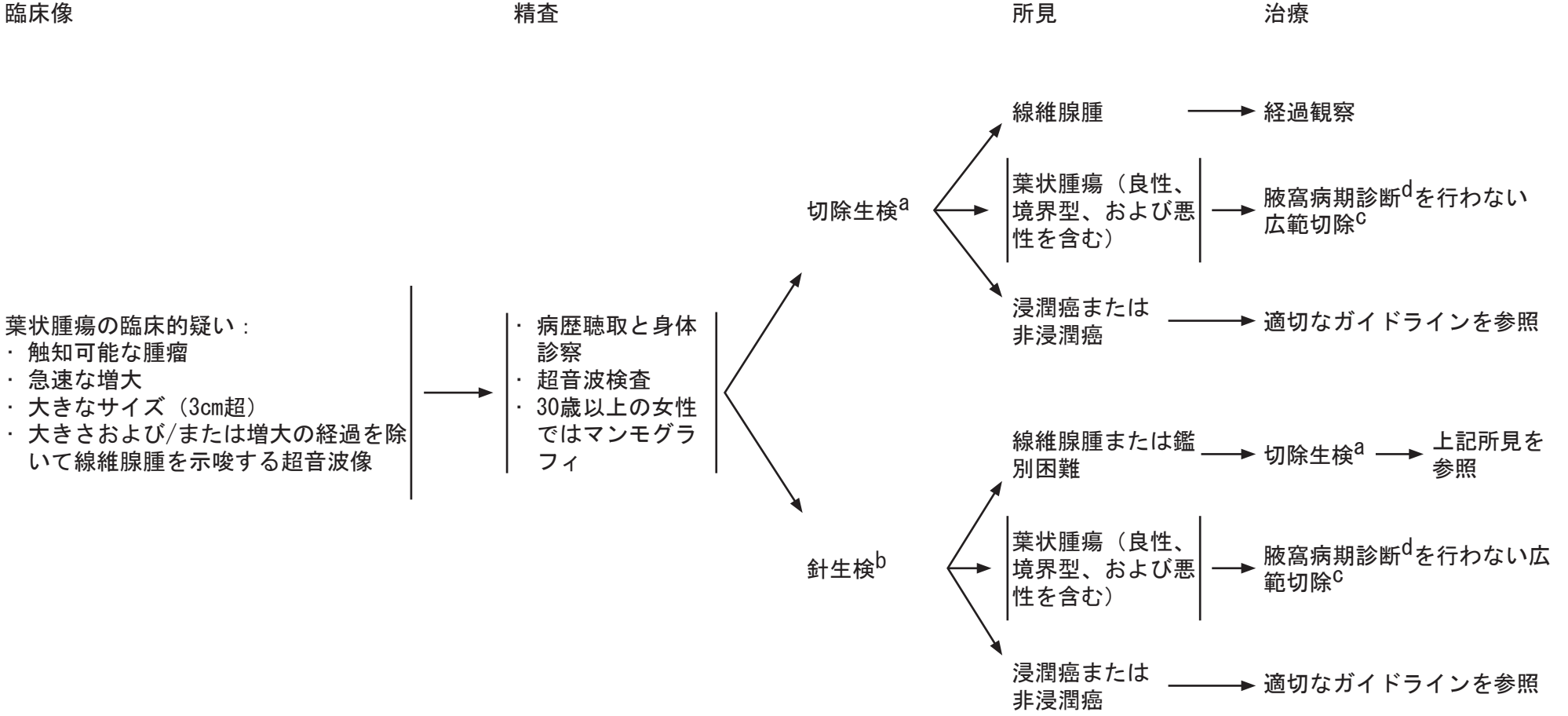
考察



a 切除生検には腫瘤の完全切除が含まれるが、手術断端確保は意図していない。

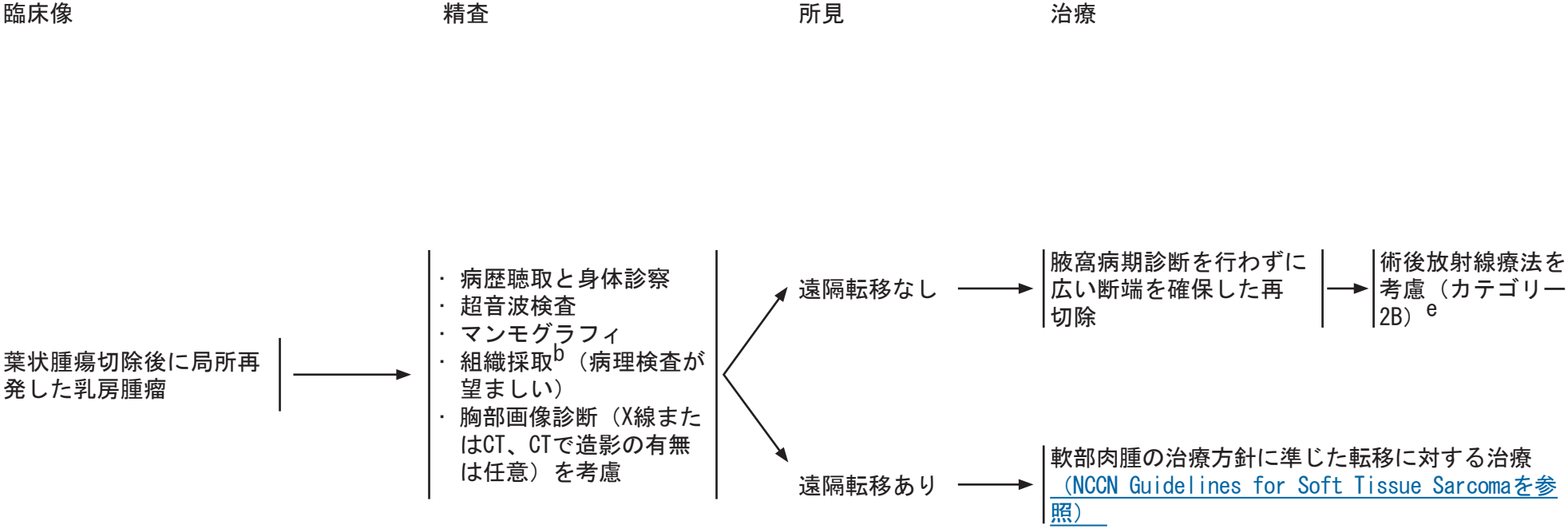
b 一部の例で、FNAまたは針生検では線維腺腫と葉状腫瘍を鑑別できないことがある。葉状腫瘍の診断に対する針生検の感度は、FNA生検より高いが、針生検でもFNA生検でも常に葉状腫瘍と線維腺腫が鑑別できるわけではない。葉状腫瘍が臨床的に疑われる場合、病理学的分類を確実に行うには、病変の切除検体が必要である。

c 広範切除とは、1cm以上の手術断端の確保を意図した切除を意味する。手術断端が狭いと局所再発のリスクが高まるが、乳房部分切除術で1cm以上の断端を達成できなくても乳房全切除術の絶対的適応とはならない。

d 葉状腫瘍に対する放射線療法を支持する前向きランダム化試験データは得られていない。ただし（救済乳房全切除術後の胸壁再発など）再々発によって深刻な病態が生じると思われる状況では、軟部肉腫の治療と同じ原則に従って放射線療法を考慮してもよい。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

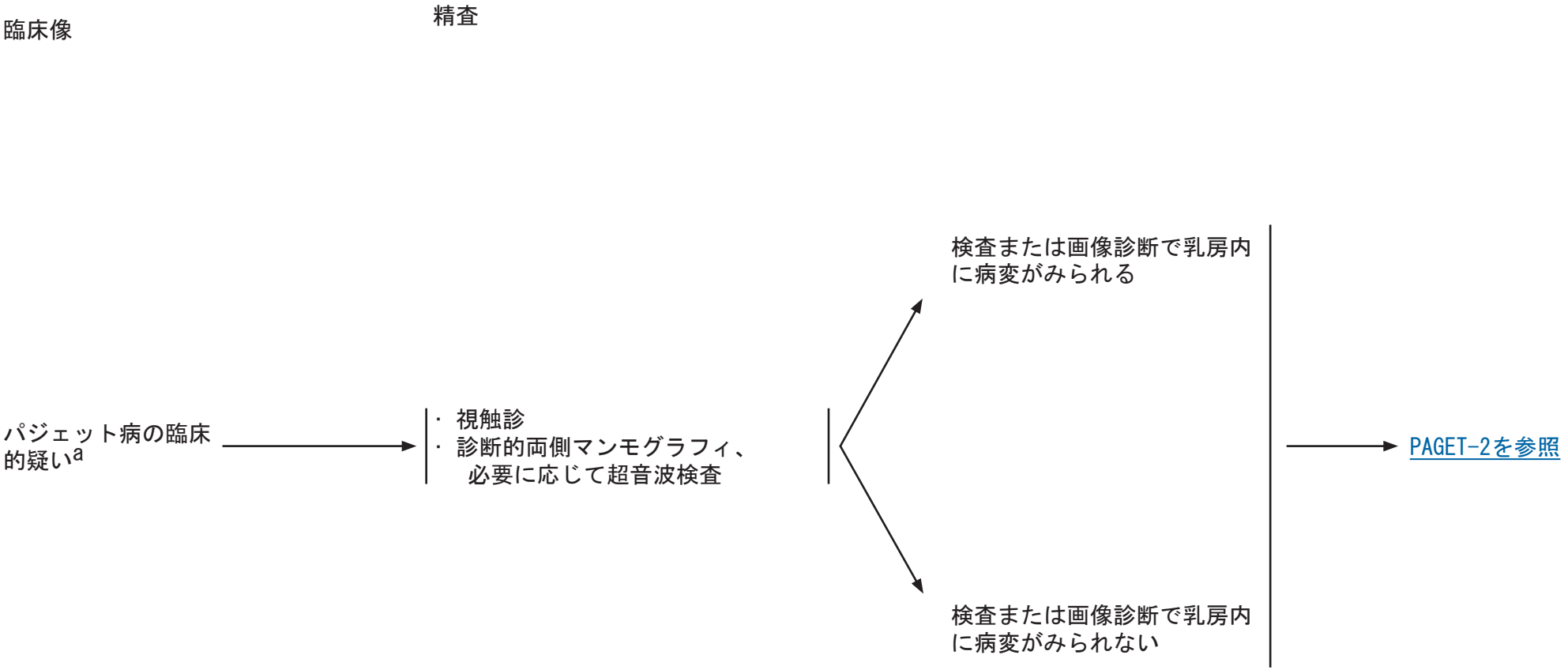
葉状腫瘍の再発



b 一部の例で、FNAまたは針生検では線維腺腫と葉状腫瘍を鑑別できないことがある。葉状腫瘍の診断に対する針生検の感度は、FNA生検より高いが、針生検でもFNA生検でも常に葉状腫瘍と線維腺腫が鑑別できるわけではない。葉状腫瘍が臨床的に疑われる場合、病理学的分類を確実に行うには、病変の切除検体が必要である。

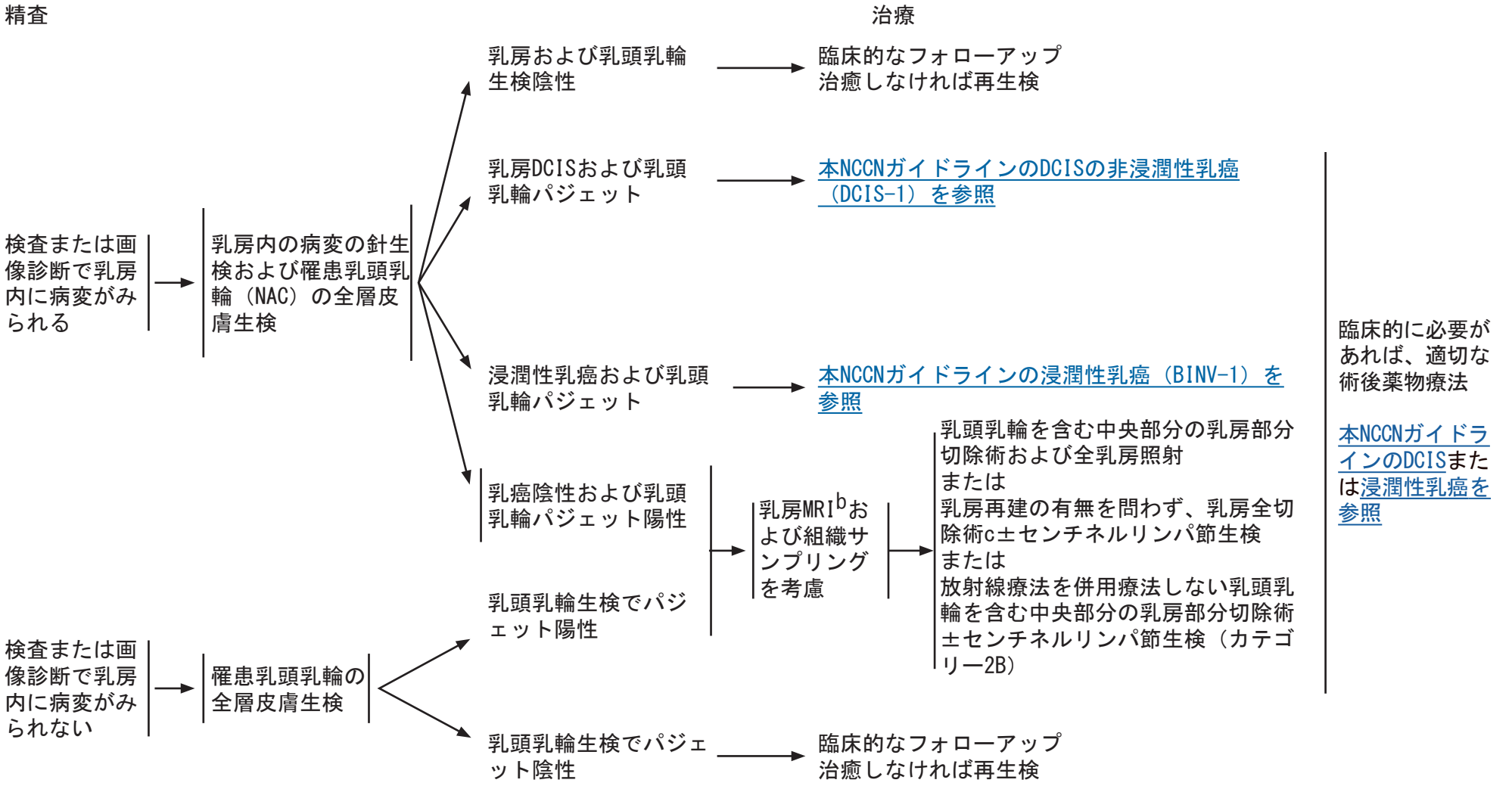
e 葉状腫瘍に対する放射線療法を支持する前向きランダム化試験データは得られていない。ただし（救済乳房全切除術後の胸壁再発など）再々発によって深刻な病態が生じると思われる状況では、軟部肉腫の治療と同じ原則に従って放射線療法を考慮してよい。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[a] 乳頭または乳輪の湿疹、潰瘍形成、出血、そう痒。

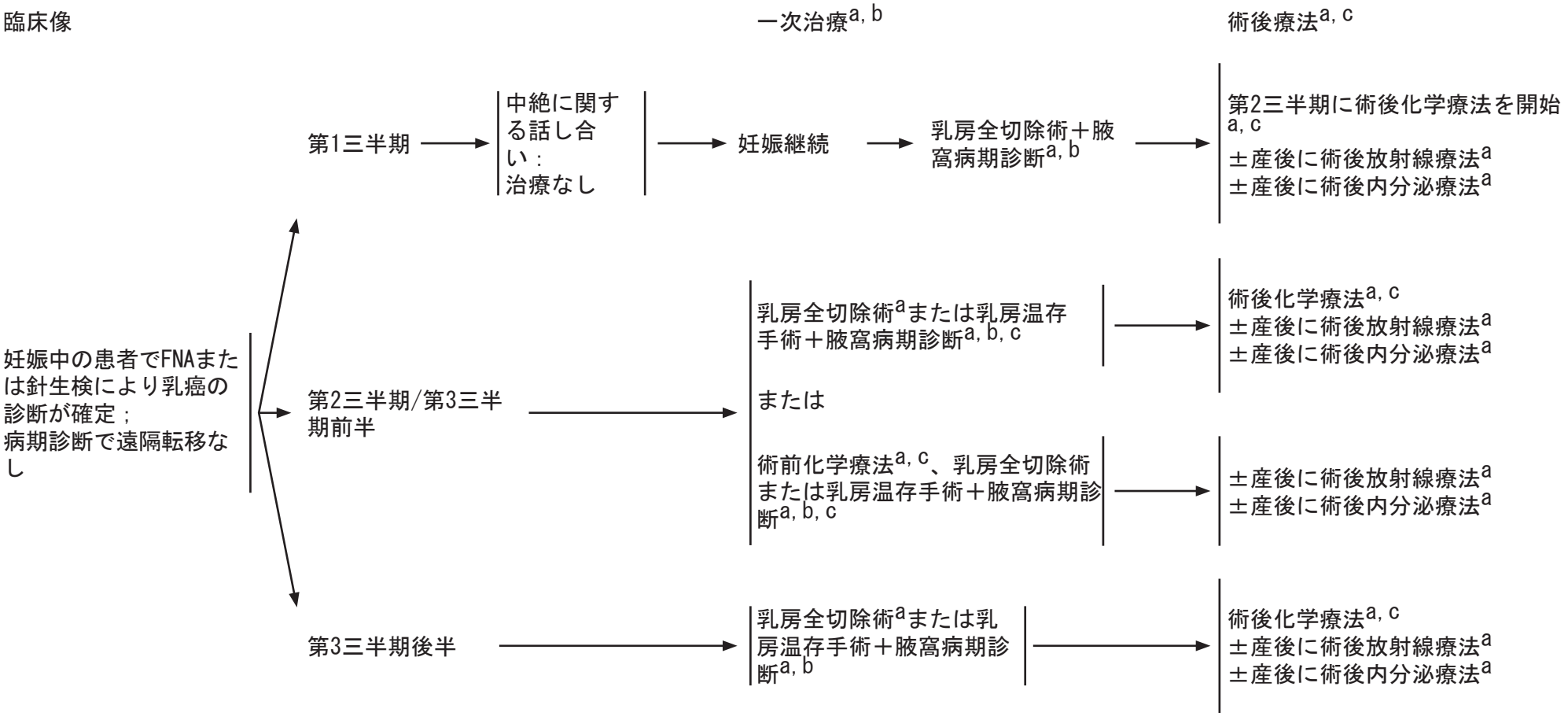
注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



b 乳房MRI検査の原則（BINV-B）を参照のこと。

c 何らかのパジェット病症状が現れている場合には、常に乳房全切除術が選択肢となる（考察を参照）。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

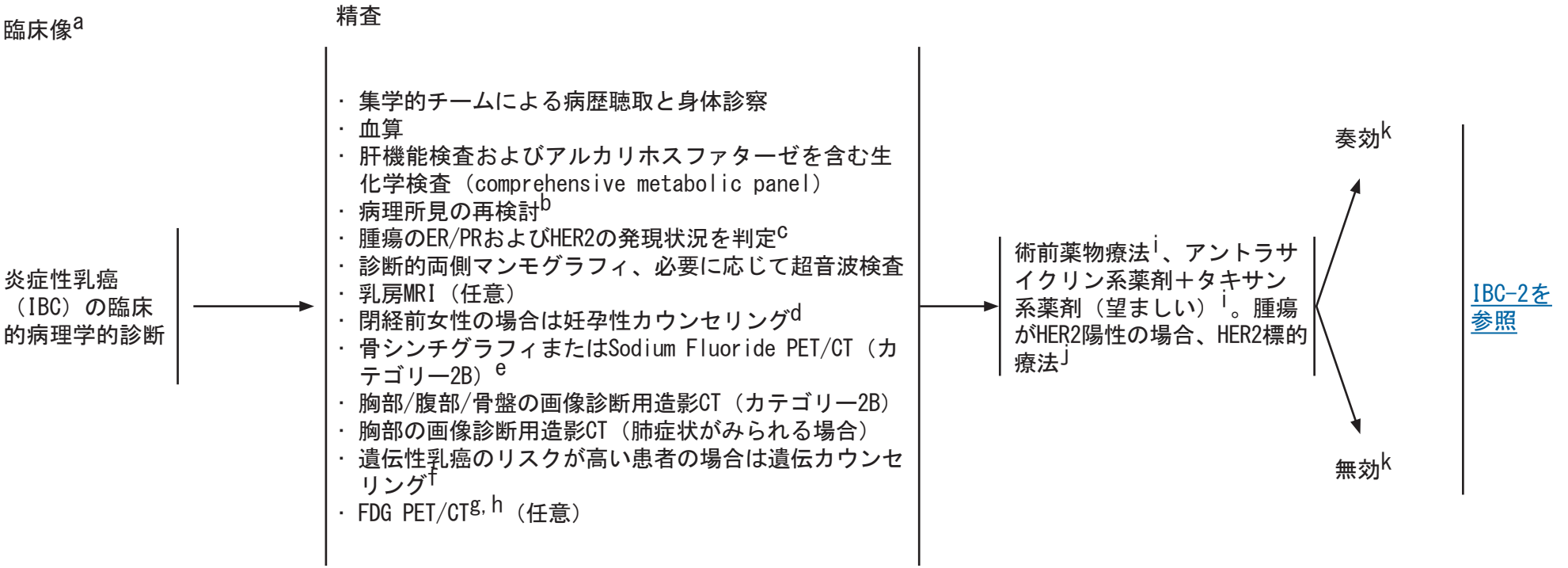


[a] 最適な局所療法および全身療法の考慮点や選択については、妊娠していない乳癌患者で推奨されているものと同様である（本ガイドラインの他のセクションを参照）。ただし、化学療法、内分泌療法および放射線療法の選択と施行時期は、患者が妊婦中か否かで異なる（考察を参照）。化学療法は妊娠の第1三半期には施行すべきでなく、放射線療法はいずれの三半期にも施行すべきでない。乳癌に対する妊娠中の化学療法の経験は、その大部分がドキソルビシン、シクロホスファミドおよびフルオロウラシルによる種々の併用レジメンから得られたものである。産後の化学療法の考慮点は、妊娠していない乳癌患者の場合と同様である。

[b] 妊娠中の青色色素の使用は禁忌であり、妊娠中のセンチネルリンパ節生検には放射標識Sulfur Colloidが安全とみられている。外科的腋窩リンパ節病期診断（BINV-D）を参照のこと。

[c] 妊娠中のタキサン系薬剤の普遍的適用を推奨できる十分な安全性データは得られていない。ただし、第1三半期後のパクリタキセル週1回投与は、疾患状態により臨床的に適応となる場合に受け入れられる。妊娠中の抗HER2療法は禁忌である。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[a] 炎症性乳癌は、浸潤性乳癌を有する女性における臨床症候群であり、紅斑と乳房皮膚の1/3以上に及ぶ浮腫（橙皮状皮膚）を特徴とする。鑑別診断には、乳房蜂窩織炎および乳腺炎が含まれる。病理学的には、皮膚病変の皮膚リンパ管侵襲が一般に認められるが、皮膚リンパ管侵襲は、炎症性乳癌の診断にとって必要条件でなく、またそれだけで十分というわけではない。

[b] 当委員会は、すべての浸潤性および非浸潤性乳癌の病理報告についてCollege of American Pathologists Protocolを支持している。http://www.cap.org。

[c] HER2検査の原則（BINV-A）を参照のこと。

[d] 妊孕性および避妊（BINV-C）を参照のこと。

[e] FDG PET/CTを施行して、PETとCTの両要素から骨転移が明白に示された場合には、骨シンチグラフィまたはSodium Fluoride PET/CTは必要ないと考えられる。

[f] NCCN「乳癌および卵巣癌における遺伝学的/家族性リスク評価」ガイドラインを参照のこと。

[g] FDG PETは診断目的のCTと同時に施行することができる。FDG PET/CTは、標準的な病期診断検査では結果が曖昧であるか疑わしい状況で最も有用となる（特に局所進行例または転移例の場合）。

[h] FDG PET/CTは、標準的な病期診断検査に加えて用いる場合、局所進行乳癌において疑われていない領域リンパ節病変や遠隔転移を同定するのにも有用となりうる。

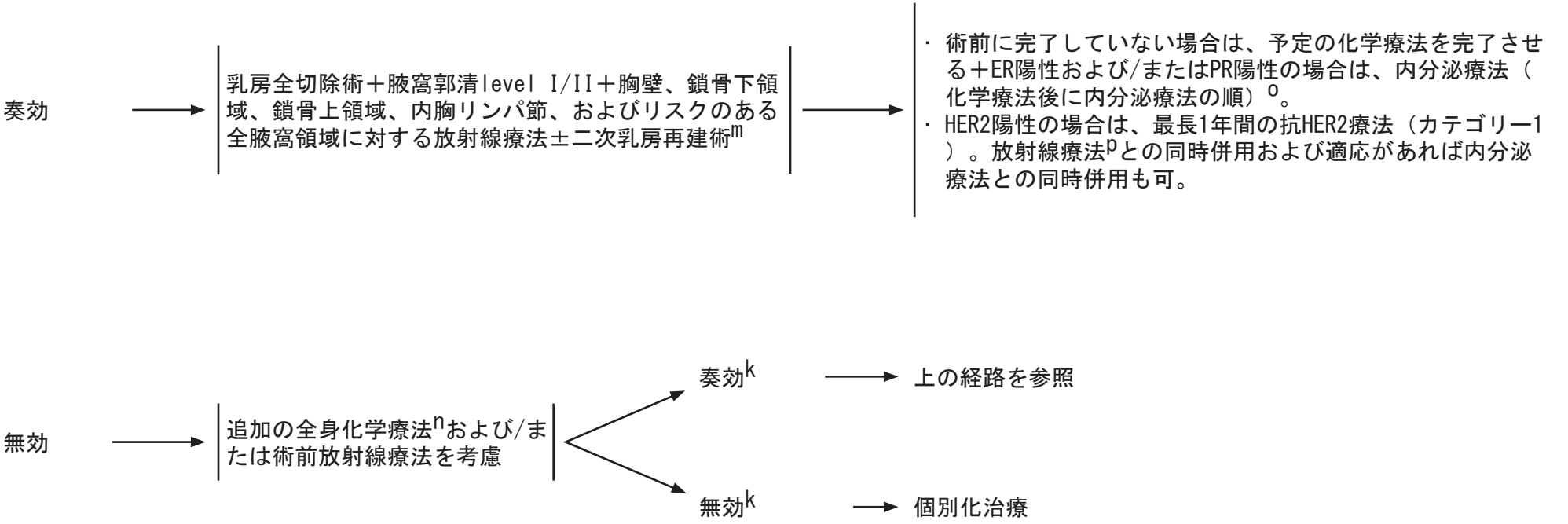
[i] 術前薬物療法/術後化学療法（BINV-K）を参照のこと。

[j] HER2陽性のIBC患者には、ペルツズマブを含むレジメンを術前投与してもよい。

[k] 乳癌の原発巣および領域リンパ節における術前薬物療法の効果を正確に評価するのは難しく、その評価には身体診察に加えて、最初の病期診断時に異常がみられた画像検査（マンモグラフィおよび/または乳房MRI）を含めるべきである。手術前の画像検査法の選択は、集学的チームによって決定されるべきである。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

治療[l]



[k] 乳癌の原発巣および領域リンパ節における術前薬物療法の効果を正確に評価するのは難しく、その評価には身体診察に加えて、最初の病期診断時に異常がみられた画像検査（マンモグラフィおよび/または乳房MRI）を含めるべきである。手術前の画像検査法の選択は、集学的チームによって決定されるべきである。

[l] IBC期の再発患者は、再発/IV期（M1）に対するガイドライン（BINV-17）に従って治療すべきである。

[m] 術後乳房再建の原則（BINV-H）を参照のこと。

[n] 再発/IV期（M1）に対する化学療法レジメン（BINV-O）および再発/IV期（M1）に対する化学療法レジメン（BINV-O）を参照のこと。

[o] 術後内分泌療法（BINV-J）を参照のこと。

[p] 放射線療法の原則（BINV-I）を参照のこと。

注：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

American Joint Committee on Cancer（AJCC）
乳癌のTNM病期分類

原発腫瘍（T） 原発腫瘍の分類は、臨床基準または病理学的基準、あるいはその両方に基づくものであるかどうかに関係なく、同じ基準により定義される。T分類は、主に浸潤癌成分の大きさに基づいている。腫瘍巣の最大寸法は、病変の体積を推定するために使用される。連続腫瘍巣の最大寸法が使用され、不連続腫瘍の小さな衛星病巣は大きさに含めない。浸潤腫瘍細胞に対する細胞線維化反応は、一般に治療前の腫瘍測定に含められるが、術前療法後にみられる密な線維化は、その進展によって残存腫瘍量が過大評価されるため、一般に病理学的測定に含められない。大きさは、1mm単位で測定する。腫瘍の大きさが、所定のT分類に対するカットオフ値よりわずかに小さいまたは大きい場合、カットオフ値に最も近い1mm単位の値に四捨五入すべきである。例えば、大きさが4.9mmの場合は5mmと報告し、2.04cmの場合は2.0cm（20mm）と報告する。この四捨五入規則の例外は、乳房腫瘍の大きさが1.0～1.4mmの場合である。このような大きさでは、四捨五入してしまうと、癌の大きさが1.0mm以下と定義される微小浸潤癌（T1mi）に分類されてしまうため、2mmに切り上げる。原発腫瘍（T）の臨床的大きさは、臨床所見（身体診察、ならびにマンモグラフィ、超音波検査、およびMRIなどの画像検査）および病理所見（肉眼または顕微鏡測定）に基づいて測定される。臨床的な腫瘍の大きさ（cT）は、特定の症例で最も正確であると判定される臨床所見に基づくべきであるが、一部の乳癌の進展は必ずしも現在の画像法で明らかになるとは限らないことに加え、腫瘍が非浸潤癌および浸潤癌の様々な集団から構成されており、これらの画像法では現時点で区別できないため、まだ幾分不正確な可能性がある。

表1. T, N, Mの定義

TX	原発腫瘍の評価ができない
T0	原発腫瘍を認めない
Tis（DCIS）*	非浸潤性乳管癌（ductal carcinoma *in situ*）
Tis（パジェット病）	乳頭のパジェット病で、下部の乳房実質中に浸潤癌および/または非浸潤癌（DCIS）を伴わないもの。パジェット病を伴った乳房実質中の癌については、パジェット病の存在を記載すべきであるが、乳腺実質の病変の大きさと性状で分類する。
T1	最大径が20mm以下の腫瘍
T1mi	最大径が1 mm以下の腫瘍
T1a	最大径が1mmを超えるが5mm以下の腫瘍（1.0mmを超えて1.9mmまでの測定値は2.0mmに切り上げる）
T1b	最大径が5mmを超えるが10mm以下の腫瘍
T1c	最大径が10 mmを超えるが20 mm以下の腫瘍
T2	最大径が20mmを超えるが50mm以下の腫瘍
T3	最大径が50mmを超える腫瘍
T4	腫瘍の大きさを問わず、胸壁および/または皮膚への直接進展を認める（潰瘍形成または皮膚結節）；真皮のみへの浸潤はT4に該当しない
T4a	胸壁への進展を認める；胸壁構造への浸潤を認めない胸筋浸潤または癒着はT4に該当しない
T4b	潰瘍形成および/または同側乳房の肉眼的衛星皮膚結節および/または皮膚の浮腫（橙皮状皮膚［peau d’orange］を含む）を認めるが、炎症性乳癌の基準は満たさない
T4c	T4aとT4bの両方に該当する
T4d	炎症性乳癌

*注：非浸潤性小葉癌（LCIS）は良性の腫瘍であり、AJCC Cancer Staging Manual第8版ではTNM病期分類から削除されている。

続く

表1. T, N, Mの定義（続き）

領域リンパ節（N）	
臨床的（cN）	
cNX*	領域リンパ節の評価ができない（例えば、摘出済みの場合）
cN0	領域リンパ節転移を認めない（画像検査または臨床検査による）
cN1	可動性の同側腋窩level I/IIリンパ節に転移を認める
cN1mi**	微小転移（細胞数が約200個で、0.2mmを超えるが、2.0mmを超えるものはない）
cN2	臨床的に固定または癒合した同側腋窩level I/IIリンパ節に転移を認めるか、*または*臨床的に明らかな腋窩リンパ節転移を認めない状況で同側内胸リンパ節に転移を認める
cN2a	相互にまたは周囲組織と固定した同側腋窩level I/IIリンパ節に転移を認める
cN2b	腋窩リンパ節に転移を認めない状況で同側内胸リンパ節に転移のみを認める
cN3	腋窩level I/IIリンパ節転移の有無を問わず、同側鎖骨下（level III腋窩）リンパ節に転移を認める； *または*腋窩level I/IIリンパ節転移とともに、同側内胸リンパ節に転移を認める； *または*腋窩や内胸リンパ節転移の有無を問わず、同側鎖骨上リンパ節に転移を認める
cN3a	同側鎖骨下リンパ節に転移を認める
cN3b	同側内胸および腋窩リンパ節に転移を認める
cN3c	同側鎖骨上リンパ節に転移を認める

病理学的（pN）	
pNX	領域リンパ節の評価ができない（例えば、病理学検索用の摘出がなされていない場合または摘出済みの場合）
pN0	領域リンパ節転移が認められないか、ITCのみが認められる
pN0(i+)	領域リンパ節にITCのみが認められる（0.2mm以下の悪性細胞集塊群）
pN0(mol+)	逆転写ポリメラーゼ連鎖反応（RT-PCR）法による分子生物学的検査で陽性；ITCは認められない
pN1	微小転移を認める；または1～3個の腋窩リンパ節に転移を認める；かつ/または臨床的に内胸リンパ節は陰性で、センチネルリンパ節生検により顕微鏡的転移または肉眼的転移を認める
pNmi	微小転移（細胞数が約200個で、0.2mmを超えるが、2.0mmを超えるものはない）
pN1a	1～3個の腋窩リンパ節に転移を認め、そのうち少なくとも1つは最大径が2.0mmを超える
pN1b	同側の内胸リンパ節（センチネルリンパ節）に転移を認めるが、ITCは認めない
pN1c	pN1aとpN1bの複合
pN2	4～9個の腋窩リンパ節に転移を認める；または腋窩リンパ節転移を認めない状況で画像検査により同側内胸リンパ節転移が陽性
pN2a	4～9個の腋窩リンパ節に転移を認める（そのうち少なくとも1つは最大径が2.0mmを超える）
pN2b	病理学的に腋窩リンパ節転移が陰性で、顕微鏡による確認の有無を問わず、臨床的に検出された同側内胸リンパ節転移を認める

注：センチネルリンパ節生検または穿刺吸引（FNA）/針生検により転移を確認したことを示すために、N分類にそれぞれ(sn)および(f)の接尾辞を追加すること。
* cNX分類は、領域リンパ節を以前に外科的に切除している場合または腋窩の身体診察の記録がない場合に控えめに使用する。
** cN1miは、まれにしか使用されないが、腫瘍切除前にセンチネルリンパ節生検を施行したケースで当てはまる場合があり、術前療法を施行した場合に認められる可能性が最も高い。

続く

表1. T, N, Mの定義（続き）

病理学的（pN）

pN3	10個以上の腋窩リンパ節に転移を認める； *または*鎖骨下（level III腋窩）リンパ節に転移を認める；または転移陽性のlevel I/II腋窩リンパ節がある状況で画像検査により同側内胸リンパ節転移が陽性； *または*4個以上の腋窩リンパ節に転移を認め、かつ臨床的に陰性の内胸リンパ節においてセンチネルリンパ節生検により顕微鏡的または肉眼的転移を認める； *または*同側鎖骨上リンパ節に転移を認める
pN3a	10個以上の腋窩リンパ節に転移を認める（少なくとも1つは2.0mmを超える）； *または*鎖骨下（level III腋窩）リンパ節に転移を認める
pN3b	cN2b所見が存在する状況（画像検査により同側腋窩リンパ節転移が陽性）でのpN1aまたはpN2a； *または*pN1b所見が存在する状況でのpN2a
pN3c	同側鎖骨上リンパ節に転移を認める

注：更なるリンパ節切除なしにセンチネルリンパ節生検またはFNA/針生検により転移を確認したことを示すために、N分類にそれぞれ(sn)および(f)の接尾辞を追加すること。

遠隔転移（M）

M0	遠隔転移の臨床および画像所見を認めない*
cM0(i+)	遠隔転移の臨床および画像所見を認めないものの、転移の症状・徴候がみられない患者の循環血中、骨髄中、その他領域リンパ節以外の組織中において、顕微鏡または分子生物学的手法により0.2mmを超えない腫瘍細胞またはtumor depositが検出される
cM1	臨床的手法および画像診断法により検出された遠隔転移を認める
pM1	遠隔臓器において組織学的に証明された転移を認める；または領域リンパ節以外であれば最大径が0.2mmを超える転移を認める

表2. AJCC解剖学的病期群

Anatomic Stage Groupの表は、バイオマーカー検査がルーチンで利用できない地域でのみ使用すべきである。
米国の癌登録では、症例報告にClinical and Pathological Prognostic Stage Groupの表を使用する必要がある。

0期	Tis	N0	M0	IIIA期	T0	N2	M0
IA期	T1	N0	M0		T1	N2	M0
IB期	T0	N1mi	M0		T2	N2	M0
	T1	N1mi	M0		T3	N1	M0
IIA期	T0	N1	M0		T3	N2	M0
	T1	N1	M0	IIIB期	T4	N0	M0
	T2	N0	M0		T4	N1	M0
IIB期	T2	N1	M0		T4	N2	M0
	T3	N0	M0	IIIC期	Any T	N3	M0
				IV期	Any T	Any N	M1

注：

1. T1にはT1miが含まれる。
2. リンパ節微小転移（N1mi）を伴うT0およびT1はIB期に分類する。
3. リンパ節微小転移（N1mi）を伴うT2、T3およびT4はN1分類を用いて分類する。
4. M0にはM0(i+)が含まれる。
5. pM0の指定は有効でなく、M0はすべて臨床診断である。
6. 術前化学療法前にM1所見を認める場合は、病期はIV期とし、術前療法に対する反応とは無関係にIV期のままとする。
7. 術後画像検査で遠隔転移の存在が明らかになった場合、病勢進行がみられない状態で、検査が診断から4ヵ月以内に実施された場合、患者が術前化学療法を受けていない場合、病期は変更されることがある。
8. 術前療法後の病期分類では、TおよびN分類に「yc」または「yp」の接頭文字を指定する。術前療法に病理学的完全奏効（pCR）を示した場合、例えばypT0ypN0cM0の場合は、解剖学的病期群は指定しない。

続く

表2. AJCC解剖学的病期群（続き）

組織学的グレード分類（G）
すべての浸潤性乳癌に対して組織学的グレードを評価すべきである。Nottingham総合組織学的グレード分類（SBRグレード分類システムのNottinghamによる改変版）が推奨され、College of American Pathologists（www.cap.orgを参照）により使用が規定されている。腫瘍の悪性度は、形態的特徴（腺管形成、核異型、較正核分裂像）を評価してそれぞれに1（良好）から3（不良）の数値を指定し、この3つのカテゴリーのスコアをすべて足し合わせることによって判定する。合計スコアが3～5ポイントはグレード1、6～7ポイントはグレード2、8～9ポイントはグレード3となる。主観的な病期分類のみの使用は推奨されない。

浸潤癌組織学的グレード分類（Scarff-Bloom-Richardson [SBR] グレード分類システムのNottingham改変版）
GX　グレードを評価できない
G1　総合組織学的グレードが低い（予後良好）；SBRスコアが3～5ポイント
G2　総合組織学的グレードが中間（予後中程度）；SBRスコアが6～7ポイント
G3　総合組織学的グレードが高い（予後不良）；SBRスコアが8～9ポイント

非浸潤性乳管癌：核異型度
GX　グレードを評価できない
G1　核異型度が低い
G2　核異型度が中程度
G3　核異型度が高い

組織型
組織型は以下の通りである：
非浸潤癌
非浸潤性乳管癌
パジェット病
浸潤癌
他に特定されない（NOS）
乳管癌
炎症性乳癌
髄様癌、NOS
間質にリンパ球浸潤を伴う髄様癌
粘液癌　　乳頭状癌（主に浸潤性微小乳頭癌）
管状癌
小葉癌
パジェット病および浸潤癌
未分化癌
扁平上皮癌
腺様嚢胞癌
分泌癌
浸潤性篩状癌

続く

イリノイ州シカゴのAmerican College of Surgeonsの許可を得て使用。この情報の出典は、Springer International Publishing発行のAJCC Cancer Staging Manual第8版（2017年）である。本表の病期分類を裏付ける完全な情報およびデータについては、www.springer.comを参照）。

表3. 予後に基づく臨床病期（Clinical Prognostic Stage）
予後に基づく臨床病期は、すべての乳癌患者の臨床分類および病期分類に適用される。病歴、身体診察、実施したあらゆる画像検査（必ずしも臨床病期分類用でなくともよい）、および関連する生検の結果に基づいて、臨床的な原発腫瘍（T）、リンパ節転移（N）および遠隔転移（M）のカテゴリーを使用する。ゲノムプロファイル情報については、手術からの病理学的情報はそれらのツールを用いて予後を確認する必要があることから、予後に基づく臨床病期には含めない。

TNM	グレード	HER2	ER	PR	病期
Tis N0 M0	任意	任意	任意	任意	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	陽性	陽性	陽性	IA期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	IB期
	G2	陽性	陽性	陽性	IA期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	IB期
	G3	陽性	陽性	陽性	IA期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	IB期
				陰性	

TNM	グレード	HER2	ER	PR	病期
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	陽性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	
	G2	陽性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	IIB期
		陰性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	
	G3	陽性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIB期
				陰性	
			陰性	陽性	
				陰性	

続く

*T1にはT1miが含まれる。
**N1にはN1miは含まれない。予後に基づく病期分類には、T1 N1mi M0およびT0 N1mi M0の分類が含まれ、これらはT1 N0 M0と予後因子の状態が同じである。

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表3. 予後に基づく臨床病期（続き）

TNM	グレード	HER2	ER	PR	病期
T2 N1*** M0 T3 N0 M0	G1	陽性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	IIB期
		陰性	陽性	陽性	IIA期
				陰性	IIB期
			陰性	陽性	
				陰性	
	G2	陽性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	IIB期
		陰性	陽性	陽性	IIA期
				陰性	IIB期
			陰性	陽性	
				陰性	IIIB期
	G3	陽性	陽性	陽性	IB期
				陰性	IIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	IIIA期
			陰性	陽性	
				陰性	IIIB期

TNM	グレード	HER2	ER	PR	病期
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	陽性	陽性	陽性	IIA期
				陰性	IIIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIA期
				陰性	IIIA期
			陰性	陽性	
				陰性	IIIB期
	G2	陽性	陽性	陽性	IIA期
				陰性	IIIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIA期
				陰性	IIIA期
			陰性	陽性	
				陰性	IIIB期
	G3	陽性	陽性	陽性	IIB期
				陰性	IIIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	IIIB期
			陰性	陽性	
				陰性	IIIC期

続く

*T1にはT1miが含まれる。
***N1にはN1miが含まれる。予後に基づく病期分類には、T2、T3、T4およびN1miが含まれ、それぞれT2 N1、T3 N1、およびT4 N1である。

表3. 予後に基づく臨床病期（続き）

TNM	グレード	HER2	ER	PR	病期
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	陽性	陽性	陽性	IIIA期
				陰性	IIIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	IIIC期
	G2	陽性	陽性	陽性	IIIA期
				陰性	IIIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	IIIC期
	G3	陽性	陽性	陽性	IIIB期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	IIIC期
			陰性	陽性	
				陰性	
Any T Any N M1	任意	任意	任意	任意	IV期

注：
1. N1miの分類には、全リンパ節の評価が必要であり、FNAまたは針生検の結果からは指定できないため、術前化学療法または内分泌療法を受ける前にセンチネルリンパ節生検を施行した状況など、原発腫瘍を切除していない状況で切除されたリンパ節の所見に基づいて臨床病期分類を行った場合にのみ、N1miは予後に基づく臨床病期分類に採用できる。
2. 原発腫瘍の所見がないリンパ節転移（例：T0 N1）または非浸潤性乳管癌（例：Tis N1）の場合は、病期群の指定にリンパ節腫瘍からのグレード、HER2、ERおよびPRに関する情報を用いるべきである。
3. ASCO/CAPの2013年HER2検査ガイドラインに基づき、ISH（FISHまたはCISH）検査によりHER2が「曖昧（equivocal）」と判定された場合は、Clinical Prognostic Stage Groupでの病期分類にはHER2「陰性」のカテゴリーを採用すべきである。
4. これらPrognostic Stage Groupの予後予測上の価値は、適切な内分泌療法および/または全身化学療法（抗HER2療法を含む）が勧められ、大半がその治療を受けた乳癌患者集団に基づく。

続く

***N1にはN1miが含まれる。予後に基づく病期分類には、T2、T3、T4およびN1miが含まれ、それぞれT2 N1、T3 N1、およびT4 N1である。

イリノイ州シカゴのAmerican College of Surgeonsの許可を得て使用。この情報の出典は、Springer International Publishing発行のAJCC Cancer Staging Manual第8版（2017年）である。本表の病期分類を裏付ける完全な情報およびデータについては、www.springer.comを参照）。

表4. 予後に基づく病理学的病期

予後に基づく病理学的病期は、初回治療として手術を受けた乳癌患者に適用される。これには、臨床病期分類に用いるすべての情報に加え、手術時の所見と外科的切除からの病理学的所見が含まれる。予後に基づく病理学的病期は、外科的切除の前に全身療法または放射線療法（術前療法）を受けた患者には適用されない。

TNM	グレード	HER2	ER	PR	病期
Tis N0 M0	任意	任意	任意	任意	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	陽性	陽性	陽性	IA期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	
	G2	陽性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	IB期
	G3	陽性	陽性	陽性	IA期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	
				陰性	
			陰性	陽性	
				陰性	IB期

TNM	グレード	HER2	ER	PR	病期
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	陽性	陽性	陽性	IA期
				陰性	IB期
			陰性	陽性	
				陰性	IIA期
		陰性	陽性	陽性	IA期
				陰性	IB期
			陰性	陽性	
				陰性	IIA期
	G2	陽性	陽性	陽性	IA期
				陰性	IB期
			陰性	陽性	
				陰性	IIA期
		陰性	陽性	陽性	IA期
				陰性	IIA期
			陰性	陽性	
				陰性	
	G3	陽性	陽性	陽性	IA期
				陰性	
			陰性	陽性	IIA期
				陰性	
		陰性	陽性	陽性	IB期
				陰性	IIA期
			陰性	陽性	
				陰性	

続く

*T1にはT1miが含まれる。

**N1にはN1miは含まれない。予後に基づく病期分類には、T1 N1mi M0およびT0 N1mi M0の分類が含まれ、これらはT1 N0 M0と予後因子の状態が同じである。

イリノイ州シカゴのAmerican College of Surgeonsの許可を得て使用。この情報の出典は、Springer International Publishing発行のAJCC Cancer Staging Manual第8版（2017年）である。本表の病期分類を裏付ける完全な情報およびデータについては、www.springer.comを参照）。

表4. 予後に基づく病理学的病期（続き）

TNM	グレード	HER2	ER	PR	病期
T2 N1*** M0 T3 N0 M0	G1	陽性	陽性	陽性	IA期
				陰性	IIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IA期
				陰性	IIB期
			陰性	陽性	
				陰性	
	G2	陽性	陽性	陽性	IB期
				陰性	IIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IB期
				陰性	IIB期
			陰性	陽性	
				陰性	
	G3	陽性	陽性	陽性	IB期
				陰性	IIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIA期
				陰性	IIB期
			陰性	陽性	
				陰性	IIIA期

TNM	グレード	HER2	ER	PR	病期
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	陽性	陽性	陽性	IB期
				陰性	IIIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IB期
				陰性	IIIA期
			陰性	陽性	
				陰性	
	G2	陽性	陽性	陽性	IB期
				陰性	IIIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IB期
				陰性	IIIA期
			陰性	陽性	
				陰性	IIIB期
	G3	陽性	陽性	陽性	IIA期
				陰性	IIIA期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIB期
				陰性	IIIA期
			陰性	陽性	
				陰性	IIIC期

続く

*T1にはT1miが含まれる。
***N1にはN1miが含まれる。予後に基づく病期分類には、T2、T3、T4およびN1miが含まれ、それぞれT2 N1、T3 N1、およびT4 N1である。

表4. 予後に基づく病理学的病期（続き）

TNM	グレード	HER2	ER	PR	病期
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	陽性	陽性	陽性	IIIA期
				陰性	IIIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIIA期
				陰性	IIIB期
			陰性	陽性	
				陰性	
	G2	陽性	陽性	陽性	IIIA期
				陰性	IIIB期
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIIA期
				陰性	IIIB期
			陰性	陽性	
				陰性	IIIC期
	G3	陽性	陽性	陽性	IIIB期
				陰性	
			陰性	陽性	
				陰性	
		陰性	陽性	陽性	IIIC期
				陰性	
			陰性	陽性	
				陰性	
Any T Any N M1	任意	任意	任意	任意	IV期

注：
1. 原発腫瘍の所見がないリンパ節浸潤（例：T0 N1）または非浸潤性乳管癌（例：Tis N1）の場合は、病期群の指定にリンパ節腫瘍からのグレード、HER2、ERおよびPRに関する情報を用いるべきである。
2. ASCO/CAPの2013年HER2検査ガイドラインに基づき、ISH（FISHまたはCISH）検査によりHER2が「曖昧（equivocal）」と判定された場合は、Pathological Prognostic Stage Groupでの病期分類にはHER2「陰性」のカテゴリーを採用すべきである。
3. これらPrognostic Stage Groupの予後予測上の価値は、適切な内分泌療法および/または全身化学療法（抗HER2療法を含む）が勧められ、大半がその治療を受けた乳癌患者集団に基づく。

表5. 予後に基づく病理学的病期分類のためのゲノムプロファイル

Oncotype DXスコアが11未満の場合…

TNM	グレード	HER2	ER	PR	病期
T1 N0 M0 T2 N0 M0	任意	陰性	陽性	任意	IA期

注：
1. 予後に基づく病理学的病期を判定するのにゲノムプロファイルの解析は必要ない。ただし、適切な治療方針を決定する際に使用するためにゲノムプロファイルを解析してもよい。HER2陰性ER陽性のT1N0M0またはT2N0M0の症例でOncotypeDx®検査を行い、再発スコアが11未満であれば、その症例は予後に基づく病理学的病期群のIA期と判定すべきである。
2. T1-2, N0, M0のHER2陰性ER陽性乳癌患者で、OncotypeDx®を行わなかった場合または行ってもOncotypeDx®スコアが得られなかったか、11以上であった場合、予後に基づく病期群は上述の解剖学的分類およびバイオマーカー分類に基づいて判定する。
3. OncotypeDx®は、Level Iの前向きデータにより、スコアが11未満の患者に対する適用が支持されていることから、予後に基づく病理学的病期の判定に組み込まれた唯一の多遺伝子パネルとなっている。病期分類システムの今後の更新では、他の多遺伝子パネルからの結果を含めて、その情報を基に予後病期群に割り付けるようになる可能性がある。ゲノムプロファイル評価のこの病期分類表における追加または削除は、特定の評価法を承認するものではなく、治療時点で得られている情報に基づく最適なゲノムプロファイル評価の臨床使用を制限すべきではない。

***N1にはN1miが含まれる。予後に基づく病期分類には、T2、T3、T4およびN1miが含まれ、それぞれT2 N1、T3 N1、およびT4 N1である。

イリノイ州シカゴのAmerican College of Surgeonsの許可を得て使用。この情報の出典は、Springer International Publishing発行のAJCC Cancer Staging Manual第8版（2017年）である。本表の病期分類を裏付ける完全な情報およびデータについては、www.springer.comを参照）。

Discussion

The DCIS section has been updated to correspond with the updated algorithms on 02/07/18. The rest of the discussion update is in progress. Last updated 05/06/16.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation)

All recommendations are considered appropriate

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Overview

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women.[1] The American Cancer Society estimates that 249,260 Americans will be diagnosed with invasive breast cancer and 40,890 will die of the disease in the United States in 2016.[2]

Historically, white women have had the highest breast cancer incidence rates among women aged 40 years and older; however, incidence rates are converging among white and African American women, particularly among women aged 50 to 59 years.[3] Since 1991, breast cancer mortality has been declining,[4,5] suggesting a benefit from the combination of early detection and more effective treatment.[6]

The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors for the disease have been established. These risk factors include: female gender; increasing patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; increased mammographic breast density; and genetic mutations such as of the *BRCA1/2* genes. However, except for female gender and increasing patient age, these risk factors are associated with only a minority of breast cancers. Women with a strong family history of breast cancer should be evaluated according to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. Women at increased risk for breast cancer (generally those with ≥1.7% 5-year risk for breast cancer using the Gail model of risk assessment[7]) may consider risk reduction strategies (see NCCN Guidelines for Breast Cancer Risk Reduction).

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium. In both the lobular and ductal epithelium, a spectrum of proliferative abnormalities may be seen, including hyperplasia, atypical hyperplasia, in situ carcinoma, and invasive carcinoma.[8] Approximately 85% to 90% of invasive carcinomas are ductal in origin.[9] The invasive ductal carcinomas include unusual variants of breast cancer, such as mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Breast Cancer, an electronic search of the PubMed database was performed to obtain key literature in Breast Cancer, published between 06/19/14 and 06/29/15, using the following search terms: Breast Cancer OR DCIS OR Inflammatory Breast Cancer OR Phyllodes. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[10]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search was examined. The data from key PubMed articles selected by the panel for review during the

Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Staging

All patients with breast cancer should be assigned a clinical stage of disease, and, if appropriate evaluation is available, a pathologic stage of disease. The routine use of staging allows for efficient identification of local treatment options, assists in identifying systemic treatment options, allows for the comparison of outcome results across institutions and clinical trials, and provides baseline prognostic information. Effective January 2010, the AJCC implemented a revision of the 7th edition of the AJCC Cancer Staging Manual containing important changes and additions to the TNM staging system for breast cancer.[11] This revision differs from the 2003 edition of the AJCC staging manual by providing more direction relating to the specific methods of clinical and pathologic tumor measurement; recommending that all invasive cancers should be assigned a combined histologic tumor grade using the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system; providing clarification of the classification of isolated tumor cells in axillary lymph node (ALN) staging; subdividing stage I into stage IA and IB based upon the presence or absence of nodal micrometastases (N0 versus N0mi+); and defining a new category of M0(i+) disease referring to tumor cells microscopically detectable in bone marrow or circulating blood or found incidentally in other tissues not exceeding 0.2 mm in patients who have no signs or symptoms of metastasis. This version of the AJCC staging manual also recommends the collection of biomarkers such as hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 [HER2] status, although these characteristics do not specifically influence assigned stage of disease.

Pathology Assessment

A central component of the treatment of breast cancer is full knowledge of extent of disease and biologic features. These factors contribute to the determination of the stage of disease, assist in the estimation of the risk that the cancer will recur, and provide information that predicts response to therapy (eg, ER, PR, HER2). These factors are determined by examination of excised tissue and are provided in a written pathology report. Accurate pathology reporting requires communication between the clinician and the pathologist relating to relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (eg, palpable, mammographically detected microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (eg, chemotherapy, radiation therapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, PR, and HER2 status). The use of consistent, unambiguous standards for reporting is strongly encouraged. Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.[12,13] Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently.

The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete and standardized reporting of

malignant specimens. CAP provides a protocol for each disease site that includes cancer case summaries (checklists) along with background documentation. These checklists form the basis for a synoptic, standardized reporting of pathologic findings. The checklists are available without charge through the CAP website at www.cap.org. Consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and the NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

ER status should be determined for all samples of ductal carcinoma in situ (DCIS), and ER and PR tumor status should be determined for all samples of invasive breast cancer. ER and PR tumor status is normally determined by immunohistochemistry (IHC) testing. Although this method is considered reliable when performed by experienced pathology personnel, there have been several reports indicating that the reliability of ER and PR determinations can vary widely from one laboratory to another.[14-16] These inter-laboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status. An NCCN Task Force and a panel of ASCO and CAP members have reviewed this topic and issued recommendations on ER and PR testing in breast cancer.[17,18] Breast cancers that have at least 1% of cells staining positive for ER should be considered ER-positive.[17-19]

Principles of HER2 Testing

Along with ER and PR, the determination of HER2 tumor status is recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible. The NCCN Breast Cancer Panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

HER2 status can be assessed by measuring the number of *HER2* gene copies using in situ hybridization (ISH) techniques, or by a complementary method in which the quantity of HER2 cell surface receptors is assessed by IHC.[20] Assignment of HER2 status based on mRNA assays or multigene arrays is not recommended. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive[21-24] as well as false-negative[21,25] HER2 test results are common. A joint panel from ASCO and CAP has issued updated HER2 testing guidelines to avoid such false-positive or false-negative results. These updated guidelines have been published in the *Archives of Pathology & Laboratory Medicine* and ASCO's *Journal of Clinical Oncology.*[26,27] The NCCN Panel endorses these updated ASCO/CAP recommendations for quality HER2 testing and has outlined these recommendations in *Principles of HER2 Testing* in the NCCN Guidelines for Breast Cancer.

HER2 testing should be performed in laboratories accredited by CAP or another equivalent authority to carry out such testing. Further, these laboratories should have standardized HER2 testing procedures in place, as well as programs to periodically evaluate the proficiency of personnel performing HER2 testing. HER2 test reports should also include information on site of tumor, specimen type, histologic type, fixation method and time, block examined, and details on the HER2 testing method(s) used. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for an individual patient.

HER2-Positive Result

Consistent with the ASCO/CAP guidelines, the NCCN Panel considers either IHC or ISH with either a single or dual probe as an acceptable method for making an initial determination of HER2 tumor status. Breast cancer tumors are classified as HER2-positive if they are scored as 3+

by an IHC method defined as uniform membrane staining for HER2 in 10% or more of tumor cells or demonstrate *HER2* gene amplification by an ISH method (single probe, average *HER2* copy number ≥6.0 signals/cell; dual probe *HER2/CEP17* ratio ≥2.0 with an average HER2 copy number ≥4.0 signals/cell; dual probe *HER2*/chromosome enumeration probe (C*EP)17* ratio ≥2.0 with an average *HER2* copy number <4.0 signals/cell; and *HER2/CEP17* ratio <2.0 with an average *HER2* copy number ≥6.0 signals/cell).

High average copy number of HER2 (≥6.0 signals/cell) is considered positive regardless of the *HER2/CEP17* ratio. The rationale cited by the joint committee for including rare scenarios such as HER2 positivity when dual probe *HER2/CEP17* ratio is greater than or equal to 2.0 and average HER2 copy number is less than 4.0 signals/cell is that the first-generation trials of adjuvant trastuzumab included a small number of patients with a *HER2*/CEP17 ratio greater than or equal to 2.0 and an average *HER2* copy number less than 4.0 signals/cell. There is no trend in these data, suggesting that these patients were not responsive to trastuzumab and the trastuzumab has a favorable safety profile.

Equivocal Result

The NCCN Panel agrees with the ASCO/CAP HER2 committee that results of IHC are equivocal if scored as IHC 2+ "based on circumferential membrane staining that is incomplete and/or weak/moderate and within greater than 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within less than or equal to 10% of the invasive tumor cells." In such cases, the panel recommends reflex testing using the ISH method on the same specimen *or* repeating tests if a new specimen is available.

Similarly, samples with equivocal results by an ISH assay (for example, single probe ISH average *HER2* copy number ≥4.0 and <6.0 signals/cell; and dual probe *HER/CEP17* ratio <2.0 with an average *HER2* copy number ≥4.0 signals/cell and <6.0 signals/cell) must be confirmed by reflex testing using the IHC method on the same specimen *or* repeating tests if a new specimen is available.

Treatment Approach

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, ALN status, tumor hormone receptor (ER/PR) content, tumor HER2 status, multi-gene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. One percent of breast cancers occur in men,[5] and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.[28,29] Patient preference is a major component of the decision-making process, especially in situations in which survival rates are equivalent among the available treatment options.

In terms of treatment, breast cancer may be divided into: 1) the pure noninvasive carcinomas, which include lobular carcinoma in situ (LCIS) and DCIS (stage 0); 2) operable, locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical stage I, stage II, and some stage IIIA tumors); 3) inoperable locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical

stage IIIB, stage IIIC, and some stage IIIA tumors); and 4) metastatic (stage IV) or recurrent carcinoma.

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from invasive carcinomas with early invasion.[30,31] Therefore, pathology review of all cases is recommended.

Bilateral diagnostic mammography should be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian. Testing for genetic mutations without formal genetic counseling is discouraged.

The goal of treatment of pure in situ carcinoma is either preventing the occurrence of invasive disease or diagnosing the development of an invasive component when still localized to the breast. Patients with invasive disease, even if microinvasive, on pathology review or during re-excision, mastectomy, or ALN staging should be treated according to the stage-appropriate guideline for invasive carcinoma.

Lobular Carcinoma in Situ
(Stage 0, Tis, N0, M0)
Workup

Recommended workup includes history and physical examination, diagnostic bilateral mammography, and pathology review.

Controversy exists regarding whether an open surgical excision should be performed of the region of LCIS diagnosed by core biopsy and that is not associated with a mammographic structural abnormality or residual mammographic calcifications. Small retrospective studies have concluded that excision following the diagnosis of LCIS on core needle biopsy is not necessary.[32-34] Other studies have shown that 17% to 27% of patients with LCIS diagnosed by core needle biopsy are upgraded to having invasive cancer or DCIS after larger excisional biopsy.[35-39] Based on core needle biopsies, it may be possible to identify subsets of patients with LCIS who can be safely spared a surgical excision.[34] There are some data of small groups of patients suggesting that LCIS subtypes, including pleomorphic LCIS and LCIS associated with necrosis, carry a risk for associated invasive carcinoma similar to DCIS. Therefore, according to the NCCN Panel, it is reasonable to perform surgical excision of LCIS found in a core biopsy to exclude an associated invasive cancer or DCIS. More than 4 foci of LCIS may also increase the risk for upstaging on surgical biopsy.[40] The NCCN Panel recommends that LCIS of the usual type (involving <4 terminal ductal lobular units in a single core) found on core biopsy, as a result of routine screening for calcifications and without imaging discordance, may be managed by imaging follow-up.

Primary Treatment

Classic LCIS does not require surgical treatment. There is evidence to support the existence of histologically aggressive variants of LCIS (eg, “pleomorphic” LCIS), which may have a greater potential than classic LCIS to develop into invasive lobular carcinoma.[41] Clinicians may consider complete excision with negative margins for pleomorphic LCIS. However, outcomes data regarding treatment of patients with pleomorphic LCIS are lacking, due in part to a paucity of histologic categorization of variants of LCIS. Therefore, recommendations on the treatment of pleomorphic LCIS as a distinct entity of LCIS have not been made by the panel (see NCCN Guidelines for Breast Screening and Diagnosis).

Patients with a confirmed diagnosis of LCIS should be counseled regarding reducing the risk of developing invasive cancer (see NCCN Guidelines for Breast Cancer Risk Reduction).

Surveillance

Follow-up of patients with LCIS includes interval history and physical examinations every 6 to 12 months. Annual diagnostic mammography is recommended in patients being followed with clinical observation; see also the NCCN Guidelines for Breast Cancer Screening and Diagnosis. Patients receiving a risk reduction agent should be monitored as described in the NCCN Guidelines for Breast Cancer Risk Reduction.

Ductal Carcinoma in Situ

(Stage 0, Tis, N0, M0)

The DCIS section and its corresponding references was updated to correspond with the updated algorithms on 02/07/18.

Workup

The recommended workup and staging of DCIS includes history and physical examination; bilateral diagnostic mammography; pathology review; determination of tumor estrogen receptor (ER) status; and MRI as indicated.

For pathology reporting, the NCCN panel endorses the College of American Pathologists Protocol for both invasive and noninvasive carcinomas of the breast.[42]

The NCCN panel recommends testing for ER status in order to determine the benefit of adjuvant endocrine therapy or risk reduction. Although the tumor HER2 status is of prognostic significance in invasive cancer, its importance in DCIS has not been elucidated. To date, studies have either found unclear or weak evidence of HER2 status as a prognostic indicator in DCIS.[43-46] The NCCN Panel has concluded that knowing the HER2 status of DCIS does not alter the management strategy and is not required DCIS.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

The role of MRI in management of DCIS remains unclear. MRI has been prospectively shown to have a sensitivity of up to 98% for high-grade DCIS.[47] In a prospective, observational study of 193 women with pure DCIS who underwent both mammography and MRI imaging preoperatively; 93 (56%) women were diagnosed by mammography and 153 (92%) were diagnosed by MRI ($P < .0001$). Of the 89 women with high-grade DCIS, 43 (48%) who were not diagnosed by mammography were diagnosed by MRI alone.[47] However, other studies suggest that MRI can overestimate the extent of disease.[48] Therefore, surgical decisions should not be not be solely based on MRI results especially when mastectomy is being contemplated. If MRI findings suggest more extensive disease than is seen on mammography such that a markedly larger resection is required for complete excision, the findings should be verified histologically through MRI-guided biopsy of the more extensive enhancement.

Studies have also been performed to determine whether the use of MRI reduces re-excision rates and decreases local recurrence in women with DCIS. No reduction in re-excision rates was seen in women undergoing lumpectomy following MRI compared with those who did not undergo preoperative MRI.[49,50]

The NCCN Panel recommends only performing breast MRI for DCIS in select circumstances where additional information is warranted during the initial workup, noting that the use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy for DCIS.

Primary Treatment

The goal of primary therapy for DCIS is to prevent progression to invasive breast carcinoma. Management strategies for DCIS treatment include surgery (mastectomy or lumpectomy), radiation therapy, and adjuvant endocrine therapy to reduce risk of recurrence.

Surgery: Excision of DCIS using a breast-conserving approach (lumpectomy) with or without whole breast radiation therapy (WBRT) or alternatively, mastectomy, are the primary treatment options for individuals with DCIS.

The choice of local treatment does not impact overall disease-related survival; therefore, the individual patient's acceptance of the potential for an increased risk of local recurrence must be considered. Post-excision mammography is valuable in confirming that an adequate excision of DCIS has been performed particularly for DCIS patients who initially present with microcalcifications.[51]

Mastectomy: Patients with DCIS and evidence of widespread disease (ie, disease involving two or more quadrants) on diagnostic mammography or other imaging, physical examination, or biopsy may require mastectomy.

Mastectomy permanently alters the lymphatic drainage pattern to the axilla, so that future performance of a sentinel lymph node biopsy (SLNB) is not technically feasible.[52,53] Therefore, for DCIS patients who intend on treatment with mastectomy, or alternatively, for local excision in an anatomic location that could compromise the lymphatic drainage pattern to the axilla (eg, tail of the breast), a SLNB procedure should *strongly* be considered at the time of definitive surgery to avoid necessitating a full axillary lymph node dissection for evaluation of the axilla.[52-55]

Complete axillary lymph node dissection (ALND) is *not* recommended unless there is pathologically documented invasive cancer or axillary lymph node metastatic disease in patients (by either biopsy or SNLB). However, a small proportion of women (about 25%) with seemingly pure DCIS on initial biopsy will have invasive breast cancer at the time of the definitive surgical procedure[56] and thus will ultimately require ALN staging.

Lumpectomy plus Whole Breast Radiation Therapy (WBRT): Breast conserving therapy (BCT) includes lumpectomy to remove the tumor with negative surgical margins followed by WBRT to eradicate any residual microscopic disease.

Several prospective randomized trials of pure DCIS have shown that the addition of WBRT after lumpectomy decreases the rate of in-breast disease recurrence, [57-64] or distant metastasis-free survival.[65] In the long term follow-up of the RTOG 9804 trial, at 7 years, the local recurrence rate was 0.9% (95% CI, 0.0%–2.2%) in the radiation therapy arm versus 6.7% (95% CI, 3.2%–9.6%) in the observation arm (HR, 0.11; 95% CI, 0.03–0.47; $P < .001$). In the subset of patients with good-risk disease features, the local recurrence rate was low with observation but was decreased significantly with the addition of radiation therapy.[64] A meta-analysis of four large multicenter randomized trials confirms the results of the individual trials, demonstrating that the addition of WBRT after lumpectomy for DCIS provides a statistically and clinically significant reduction in ipsilateral breast events (HR [hazard ratio], 0.49; 95% CI; 0.41–0.58, $P < .00001$).[66] However, these trials did not show that the addition of RT has an overall survival benefit. The long-term follow-up of the NSABP B-17 showed that at 15 years, radiation therapy resulted in a 52% reduction of ipsilateral invasive recurrence compared with excision alone (HR, 0.48; 95% CI, 0.33–0.69, $P < .001$).[63] However, overall survival (OS) and cumulative all-cause mortality rates through 15 years were similar between the two groups (HR for death, 1.08; 95% CI, 0.79–1.48).[63] Similar findings were reported by a large observational study of the SEER database that included 108,196 patients with DCIS.[67] In a subgroup analysis at 10 years, of 60,000 women treated with breast-conserving therapy, with or without radiation therapy, radiation therapy was associated with a 50% reduction in the risk of ipsilateral recurrence (adjusted HR, 0.47 [95% CI, 0.42–0.53]; $P < .001$), however, breast cancer-specific mortality was found to be similar (HR, 0.86 [95% CI, 0.67–1.10]; $P = .22$).[67]

More recently, in a population-based study, the use of WBRT in patients with higher-risk DCIS (eg higher nuclear grade, younger age, and larger tumor size) was demonstrated to be associated with a modest, but statistically significant improvement in survival.[68]

RT Boost: The use of RT boost has been demonstrated to provide a small but statistically significant reduction in IBTR risk (4% at 20 years) in all age groups for invasive breast cancers.[69-72]

Recently, a pooled analysis of patient-level data from 10 academic institutions evaluated outcomes of pure DCIS patients, all treated with lumpectomy and WBRT (n = 4131) who either received RT boost with a median dose of 14 Gy (n = 2661) or received no boost (n = 1470). The median follow-up of patients was 9 years. A decrease in IBTR was seen in patients who received boost compared with those who did not at 5 years (97.1% vs 96.3%), 10 years (94.1% vs 92.5%), and 15 years (91.6% vs 88.0%) (*P* = .0389 for all). The use of RT boost was associated with significantly decreased IBTR across the entire cohort of patients (hazard ratio [HR], 0.73; 95% CI, 0.57-0.94; *P* = .01).[73] In a multivariate analysis that took into account factors associated with lower IBTR, including grade, ER positive status, use of adjuvant tamoxifen, margin status, and age, the benefit of RT boost still remained statistically significant (hazard ratio, 0.69; 95% confidence interval [CI], 0.53 - 0.91; *P* < .010).[73] Even in patients considered very low risk based on negative margins status (defined as ink on tumor as per National Surgical Adjuvant Breast and Bowel Project definition, or margins <2 mm as per SSO/ASTRO/ASCO definition), the RT boost remained statistically significant for decreasing the rate of local relapse. Similar to invasive cancers, though RT boost was beneficial in all age groups studied, the magnitude of the absolute benefit of the boost was greatest in younger patients. Two ongoing randomized, phase 3 trials are studying whether an RT boost reduces recurrence in patients with DCIS (ClinicalTrials.gov Identifiers: NCT00470236 and NCT00907868).

While considering RT boost for DCIS, the NCCN panel recommends an individualized approach based on patient preference and other factors such as longevity.

Lumpectomy alone without WBRT: Several trials have examined omission of RT after lumpectomy in carefully selected, low-risk patients. There are retrospective series suggesting that selected patients have a low risk of in-breast recurrence when treated with excision alone (without WBRT).[74-77] For example, in one retrospective review, 10-year disease-free survival (DFS) rates of 186 patients with DCIS treated with lumpectomy alone was 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.[74]

In another retrospective study of 215 patients with DCIS treated with lumpectomy without radiation therapy, endocrine therapy, or chemotherapy, the recurrence rate over 8 years was 0%, 21.5%, and 32.1% in patients with low-, intermediate- or high-risk DCIS, respectively.[75]

A multi-Institutional, non-randomized, prospective study of selected patients with low-risk DCIS treated without radiation has also provided some support for the use of excision without radiation in the treatment of DCIS.[78] Patients were enrolled onto one of two low-risk cohorts: a) low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller (n = 561); or b) high-grade DCIS, tumor size 1 cm or smaller (n = 104). Protocol specifications included excision of the DCIS tumor with a minimum negative margin width of at least 3 mm. Only 30% of the patients received tamoxifen. Of note, margins were substantially wider than the 3 mm protocol requirement in many patients (ie- the

low/intermediate-risk patient group margins were ≥ 5 mm in 62% of patients and >10 mm or no tumor on re-excision in 48 % of patients).[78] Although the rate of IBTR were acceptably low for the low-/intermediate grade group at the 5 years, at a median follow-up time of 12.3 years, the rates of developing an IBTR were 14.4% for low/intermediate-grade and 24.6% for high grade DCIS (*P* = .003). This suggests that IBTR events may be delayed but not prevented in the seemingly low-risk population.

Therefore the NCCN panel concluded that for DCIS patients treated with lumpectomy alone (without radiation), irrespective of margin width, the risk of IBTR is substantially higher than treatment with excision followed by whole breast radiation therapy (even for predefined low-risk subsets of DCIS patients).

Margin status after breast conserving therapy:

Prospective randomized trials have not been carried out to analyze whether wider margins can replace the need for radiation therapy for DCIS. Results from a retrospective study of 445 patients with pure DCIS treated by excision alone indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins less than 1 mm and greater than or equal to 10 mm.[79] In a meta-analysis of 4660 patients with DCIS treated with breast-conserving surgery and radiation, a surgical margin of less than 2 mm was associated with increased rates of IBTR compared with margins of 2 mm, although no significant differences were observed when margins of greater than 2 mm to 5 mm or greater than 5 mm were compared with 2-mm margins.[80]

A fairly recent study retrospectively reviewed a database of 2996 patients with DCIS who underwent breast-conserving surgery to investigate the association between margin width and recurrence, controlling all other characteristics.[81] Wider margins were significantly associated with a lower rate of recurrence only in women who did not receive radiation therapy (*P* < .0001), but not in those treated with radiation (*P* = .95).[81]

According to the 2016 guidelines by SSO/ASTRO/ASCO, the use of at least 2 mm margin in DCIS treated with WBRT is associated with low rates of ipsilateral breast tumor recurrence (IBTR).[82] Additional factors to consider in assessing adequacy of excision for DCIS include presence of residual calcifications, which margin is close (anterior against skin or posterior against muscle versus medial, superior, inferior or lateral), and life expectancy of the patient. Notably, in situations where DCIS is admixed with invasive carcinoma, SSO/ASTRO/ASCO guidelines support “no tumor on ink” as an adequate margin applying to both the invasive and noninvasive components in this mixed tumor scenario.

NCCN Recommendations for Primary Treatment of DCIS

Trials are ongoing to determine if there might be a selected favorable biology DCIS sub-group where surgical excision is not required. Until such time that definitive evidence regarding the safety of this non-surgical approach is demonstrated, the NCCN panel continues to recommend surgical excision for DCIS. According to the NCCN Panel, primary treatment options for women with DCIS along with their respective categories of consensus are: lumpectomy plus whole breast radiation therapy with or without boost (category 1); total mastectomy, with or without SLNB with optional reconstruction (category 2A); or lumpectomy alone (category 2B). The option of lumpectomy alone should be considered only in cases where the patient and the

physician view the individual as having a low risk of disease recurrence.

Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (see *Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy* in the NCCN Guidelines for Breast Cancer). Women treated with mastectomy are appropriate candidates for breast reconstruction (see *Principles of Breast Reconstruction Following Surgery* in the NCCN Guidelines for Breast Cancer).

According to the NCCN Panel, complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography should also be performed whenever uncertainty about adequacy of excision remains. Clips are used to demarcate the biopsy area because DCIS may be clinically occult and further surgery may be required pending the margin status review by pathology.

The NCCN Panel accepts the definitions of negative margins after BCS from the 2016 SSO/ASTRO/ASCO Guidelines for DCIS.[82] For pure DCIS treated by BCS and whole breast radiation therapy treatment (WBRT), margins of at least 2 mm are associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths in patients receiving WBRT. The routine practice of obtaining negative margin widths wider than 2 mm is not supported by the evidence. An analysis of specimen margins and specimen radiographs should be performed to ensure that all mammographically detectable DCIS has been excised. In addition, a post-excision mammogram should be considered where appropriate (eg, the mass and/or microcalcifications are not clearly within the specimen).

Management of DCIS after Primary Treatment

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The Breast Cancer Prevention Trial performed by National Surgical Adjuvant Breast and Bowel Project (NSABP) showed a 75% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen.[83,84] These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.[85] The Early Breast Cancer Trialists' Collaborative Group (*EBCTCG*) overview analysis showed that, with 5 years of tamoxifen therapy, women with ER-positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.[4]

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery and radiation therapy. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or tamoxifen. At a median follow-up of 13.6 years, patients who received tamoxifen had a 3.4% absolute reduction in ipsilateral in-breast tumor recurrence risk (HR, 0.30; 95% CI, 0.21–0.42; $P < .001$) and a 3.2% absolute reduction in contralateral breast cancers (HR, 0.68; 95% CI, 0.48–0.95; $P = .023$).[63] The women receiving tamoxifen had a 10-year cumulative rate of 4.6% for invasive and 5.6% for noninvasive breast cancers in the ipsilateral breast compared with 7.3% for invasive and 7.2% for noninvasive breast cancers in placebo-treated women. The cumulative 10-year frequency of invasive and noninvasive breast cancer in the contralateral breast was 6.9% and 4.7% in the placebo and tamoxifen groups, respectively. No differences in OS were noted. A retrospective analysis of ER expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms

of risk reduction for ipsilateral and contralateral breast cancer development following breast-conserving therapy.[86]

A phase III trial for women with excised DCIS randomized subjects in a 2 x 2 fashion to tamoxifen or not and whole breast radiation therapy or not.[62] With 12.7 years of median follow-up, the use of tamoxifen decreased all new breast events (HR, 0.71; 95% CI, 0.58–0.88; *P* = .002). The use of tamoxifen decreased ipsilateral and contralateral breast events in the subjects not given whole breast radiotherapy (ipsilateral HR, 0.77; 95% CI, 0.59–0.98; contralateral HR, 0.27; 95% CI, 0.12–0.59), but not in those receiving whole breast radiotherapy (ipsilateral HR, 0.93; 95% CI, 0.50–1.75; *P* = .80; contralateral HR, 0.99; 95% CI, 0.39–2.49; *P* = 1.0).

In women with ER-positive and/or PR-positive DCIS treated by wide local excision with or without breast radiotherapy, a large, randomized, double-blind, placebo-controlled trial (IBIS-II) compared anastrozole (n = 1471) with tamoxifen (n = 1509). The results demonstrated non-inferiority of anastrozole to tamoxifen.[87] After a median follow-up of 7.2 years, 67 recurrences were reported with anastrozole versus 77 for tamoxifen; HR 0.89 [95% CI, 0.64–1.23]. A total 33 deaths were recorded for anastrozole and 36 for tamoxifen; HR 0.9393 [95% CI, 0.58–1.50, *P* = .78).[87] Although the number of women reporting any adverse event was similar between anastrozole (1323 women, 91%) and tamoxifen (1379 women, 93%); the side-effect profiles of the two drugs were different. There were more fractures, musculoskeletal events, hypercholesterolemia, and strokes reported with anastrozole and more muscle spasms, gynecological cancers and symptoms, vasomotor symptoms, and deep vein thromboses reported with tamoxifen.

The NSABP B-35 study randomly assigned 3,104 postmenopausal patients to tamoxifen or anastrozole for 5 years. All patients received breast radiotherapy. Prior to being randomly assigned, patients were stratified by age—younger or older than age 60. The primary endpoint was breast cancer–free interval.[88] Anastrozole treatment resulted in an overall statistically significant decrease in breast cancer-free interval events compared with tamoxifen (HR, 0.73 [95% CI, 0.56–0.96], *P* = .0234). The significant difference in breast cancer-free interval between the two treatments was apparent in the study only after 5 years of follow-up. The estimated percentage of patients with a 10-year breast cancer-free interval was 89.1% in the tamoxifen group and 93.1% in the anastrozole group.[88] In addition, anastrozole resulted in further improvement in breast cancer-free interval, in younger postmenopausal patients (less than 60 years old). With respect to adverse effects, the overall incidence of thrombosis or embolism was higher in the tamoxifen group while the anastrozole group had slightly more cases of arthralgia and myalgia.[88]

The results of the IBIS-II and the NSAP-B-35 studies indicate that anastrozole provides at least a comparable benefit as adjuvant treatment for postmenopausal women with hormone-receptor-positive DCIS, with a different toxicity profile.

NCCN Recommendations for Management of DCIS after Primary Treatment

According to the NCCN Panel, endocrine therapy, with tamoxifen (for premenopausal and postmenopausal women) or an aromatase inhibitor (for postmenopausal women especially those under 60 years of age or in those with concerns of embolism), may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with ER-positive DCIS treated with breast-conserving therapy (category 1 for those undergoing breast-conserving surgery followed by radiation

therapy; category 2A for those undergoing excision alone). The benefit of endocrine therapy for ER-negative DCIS is not known.

Strategies for reducing the risk of recurrence to the contralateral breast are described in the NCCN Guidelines for Breast Cancer Risk Reduction.

Invasive Breast Cancer

Stage I, IIA, IIB, or III A (T3, N1, M0)

Workup

The recommended workup of localized invasive breast cancer includes: history and physical exam; bilateral diagnostic mammography; breast ultrasonography, if necessary; determination of tumor hormone receptor status (ER and PR determinations); determination of HER2–receptor status; and pathology review. Complete blood count (CBC) and liver function tests (LFTs) have no added benefit in the detection of underlying metastatic disease in asymptomatic early-stage breast cancer patients.[89] In addition, monitoring of disease relapse with any tumor markers is *not* recommended.

Use of MRI is optional and is not universally recommended by experts in the field. Breast MRI advocates note its high sensitivity for evaluation of extent of disease, particularly for invasive cancer and in dense breasts where mammographically occult disease is more likely to elude preoperative detection. MRI detractors note that MRI has a high percentage of false-positive findings resulting in further diagnostic workup in many circumstances including MRI-guided biopsy[90-92] MRI findings tend to overestimate extent of disease[93] resulting in increase in frequency of mastectomies.[94-97]

MRI findings alone are insufficient to determine whether breast conservation therapy is optimal as additional tissue sampling is needed to verify true malignant disease warranting excision. MRI use may increase mastectomy rates by identifying mammographically occult disease satellites that would have been adequately treated with post-lumpectomy radiation had the disease remained undiscovered without MRI.[97]

Two prospective randomized studies have examined the utility of pre-operative MRI in determining disease extent, and neither demonstrated improvement in rates of post-lumpectomy re-excision.[98,99] Retrospective review of utility MRI showed conflicting outcome results, one with benefit[100] and another without.[101] One systematic review[92] documented that breast MRI staging altered surgical treatment in 7.8% to 33.3% of women,[92] however no differences in local recurrence or survival have yet been demonstrated. In addition, there is no evidence that use of breast MRI increases rates of margin-negative resection.[102,103]

If breast MRI imaging is performed, a dedicated breast coil, an imaging team experienced with breast MRI guided biopsy, and multidisciplinary treatment team are the standard of care. Clinically positive axillary nodes and occult primary breast cancer or Paget's disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination are specific indications for breast MRI imaging. MRI may also be useful for the evaluation of breast cancer response to preoperative systemic therapy and to assess the potential for breast-conserving therapy.

Pathology Assessment: Full knowledge of extent of disease and biologic features is central to the treatment of breast cancer. Several factors contribute to the determination of the disease staging, recurrence risk assessment, and predictive response (ie, ER, PR, HER2). The excised tissue detailing the written pathology report details these key factors. The accuracy of pathology reporting requires communication between the clinician and the pathologist relating pertinent patient history, prior breast biopsies, prior chest irradiation, pregnancy status, biopsy characteristics (ie, palpable, mammographically detected microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (ie, chemotherapy, radiation therapy).

The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, PR, and HER2 status). Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.[12,13] Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently. CAP has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens (www.cap.org). The NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

Genetic counseling: For patients considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, genetic counseling is recommended

Distress Assessment: Levels of distress may vary in patients and should be addressed individually. Psychological distress can be impacted by body image and other factors. Younger women have higher rates of psychosocial distress than women diagnosed at older ages.[104-108] The NCCN Breast Cancer Panel recommends accessing for distress in patients newly diagnosed with breast cancer.

Fertility Counseling: Numerous epidemiologic studies have demonstrated that child-bearing after treatment for invasive breast cancer does not increase rates of recurrence or death from breast cancer.[109] The offspring of pregnancies after treatment for breast cancer do not have an increased rate of birth defects or other serious childhood illness. However, treatment for breast cancer, especially with cytotoxic agents, may impair fertility.

Many women, especially those younger than age 35, regain menstrual function within 2 years of completing chemotherapy.[110] Resumption of menses does not necessarily correlate with fertility, and fertility may be preserved without menses. All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies.

A decision for fertility preservation should include multiple factors such as patient preference, tumor stage and biology, age of the patient, risk of premature ovarian failure based on anticipated type and duration of chemotherapy and/or endocrine therapy, as well as the timing and duration allowed for fertility preservation.

Several studies report lower rates of fertility discussion among female patients with cancer[111-113] despite the updated ASCO guidelines stating that patients should not be excluded from consideration for discussion of fertility preservation for any reason, including parity, prognosis, age, and socioeconomic status.[114] The NCCN Panel recommends that all women of childbearing potential should have a discussion with their treating physicians. Patients who desire to bear children after systemic therapy should be referred to a fertility specialist prior to initiating systemic (chemotherapy or endocrine) therapy.[114-120]

Randomized trials have demonstrated that GnRH agonists (such as goserelin) administered prior to initiating chemotherapy and then administered concurrently with adjuvant chemotherapy protect against ovarian failure and reduce the risk of early menopause.[121-124] In one trial goserelin improved the probability of pregnancy from 11% to 21% in patients with hormone receptor-negative early-stage breast cancer.[124] Smaller historical experiences in patients with hormone receptor-positive disease have conflicting results with respect to the protective effects of GnRH agonists in fertility preservation.

Patients should be informed of all the various modalities available to minimize gonadal damage and preserve ovarian function and future fertility. The fertility specialist should discuss specifics of fertility preservation options inclusive of types of hormonal interventions and risks involved with ovarian stimulation, embryo or oocyte cryopreservation, and other investigational options, as well as the probability of successful gestation and childbirth.[125,126]

Combining the various modalities for a specific patient may increase the odds of preservation of future fertility. It is important for fetal safety that women actively avoid becoming pregnant during breast cancer treatment. Also see NCCN Guidelines for Adolescent and Young Adult Oncology.

Additional Workup

The panel has re-iterated that routine systemic imaging is *not* indicated for patients with early breast cancer *in the absence* of signs/symptoms of metastatic disease.[127] These recommendations are based on studies showing no additional value of these tests in patients with early-stage disease.[128-130] In one study, metastases were identified by bone scan in 5.1%, 5.6%, and 14% of patients with stage I, II, and III disease, respectively, and no evidence of metastasis was detected by liver ultrasonography or chest radiography in patients with stage I or II disease.[128] For patients with stage III breast cancer, the prevalence of a positive liver ultrasound and positive chest x-ray was 6% and 7%, respectively.[128]

For patients presenting with disease confined to the breast (stage I to II) the NCCN Panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients who present with locally advanced (T3 N1-3 M0) disease and in those with signs or symptoms suspicious for metastatic disease.

CBCs and LFTs may be considered if the patient is a candidate for preoperative systemic therapy, or if otherwise clinically indicated. Additional tests may be considered only based on the signs and symptoms.

A chest diagnostic CT is indicated only if pulmonary symptoms (ie, cough or hemoptysis) are present. Likewise, abdominal imaging using diagnostic CT or MRI is indicated if the patient has elevated alkaline phosphatase, abnormal results on LFTs, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis.

A bone scan is indicated in patients presenting with localized bone pain or elevated alkaline phosphatase. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III (T3 N1) breast cancer. The recommendation against the use of PET scanning is supported by the high false-negative rate in the detection of lesions that are small (<1 cm) and/or low grade, the low sensitivity for detection of axillary nodal metastases, the low prior probability of these patients having detectable metastatic disease, and the high rate of false-positive scans.[131-134]

FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

Locoregional Treatment

Surgery

In general, patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) with or without radiation therapy.

Following local treatment, adjuvant systemic therapy may be offered based on primary tumor characteristics, such as tumor size, grade, lymph node involvement, ER/PR status, and expression of HER2-receptor.

Several randomized trials document that mastectomy is equivalent to breast-conserving therapy (lumpectomy with whole breast irradiation) with respect to survival as primary breast local treatment for the majority of women with stage I and stage II breast cancers (category 1).[135-139]

After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN Panel notes that benefit of lumpectomy is predicated on achieving pathologically negative margins after resection. The NCCN Panel accepts the most recent definition outlined in the guidelines established by the Society of Surgical Oncology (SSO)/American Society for Radiation Oncology (ASTRO) of no ink on a tumor as the standard for negative surgical margins for invasive cancer (with or without a component of DCIS).[140]

If margins remain positive after further surgical re-excision(s), then mastectomy may be required for optimal local disease control.

In order to adequately assess margins following surgery, the panel recommends that the surgical specimens be directionally oriented and that the pathologist provide descriptions of the gross and microscopic margin status and the distance, orientation, and type of tumor (invasive cancer or pure DCIS) in relation to the closest margin. Marking the tumor bed with clips facilitates accurate planning of the radiation boost field, where appropriate. It may be reasonable to treat selected patients with invasive cancer (without extensive intraductal component) despite a microscopically focally positive margin with breast conservation therapy.

Breast-Conserving Therapy (Lumpectomy)

Lumpectomy allows patients to preserve their breast without sacrificing oncologic outcome. Lumpectomy is contraindicated for patients who are pregnant and would require radiation during pregnancy; have diffuse suspicious or malignant-appearing microcalcifications on mammography; have widespread disease that cannot be incorporated by local excision through a single incision with a satisfactory cosmetic result; or have diffusely positive pathologic margins. Relative contraindications to lumpectomy include previous radiation therapy to the breast or chest wall; active connective tissue disease involving the skin (especially scleroderma and lupus), tumors greater than 5 cm (category 2B), and positive pathologic margins.

Several studies of women with early-stage breast cancer treated with lumpectomy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrences after lumpectomy.[141-143] Risk factors, such as a family history of breast cancer or a genetic predisposition to breast cancer (ie, BRCA1/2 or other cancer-predisposing mutation), are more likely to exist in the population of young women with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.[144] Studies have shown that survival outcomes for young women with breast cancer receiving either lumpectomy or mastectomy are similar.[137,138,145-147] Some recent studies show improved survival[148-150] and fewer post-surgical complications[151] with lumpectomy.

Mastectomy

Mastectomy is indicated for patients who are not candidates for lumpectomy and those who choose to undergo this procedure over lumpectomy.

Only limited data are available on the survival impact of risk-reducing contralateral mastectomy in women with a unilateral breast cancer.[152] Analysis of women included in the SEER database treated with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral mastectomy performed at the time of treatment of a unilateral cancer was associated with a reduction in breast cancer-specific mortality only in the population of young women (18–49 years of age) with stage I/II, ER-negative breast cancer (HR, 0.68; 95% CI, 0.53–0.88; *P* = .004).[153] The 5-year breast cancer survival for this group was *slightly* improved with contralateral mastectomy versus without (88.5% vs. 83.7%, difference = 4.8%).[153] These differences observed in retrospective analysis could be due to selection bias among patients who chose risk-reducing contralateral mastectomy.[154] A statistical simulation of survival outcomes after risk-reducing contralateral mastectomy among women with stage I or II breast cancer with no *BRCA* mutation found that the absolute 20-year survival benefit from risk-reducing contralateral mastectomy was less than 1% among all age, ER status, and cancer stage groups.[155] Data from a recent meta-analysis found no absolute reduction in risk of distant metastases with risk-reduction mastectomy.[156] Furthermore, among patients with unilateral breast cancer who have an increased familial/genetic risk, although a decrease in metastatic contralateral breast cancer incidence was observed in those who received risk-reducing contralateral mastectomy, no improvement was seen in OS of these patients.[156]

The panel recommends that women with breast cancer who are less than or equal to 35 years or premenopausal and carriers of a known *BRCA1/2* mutation consider additional risk reduction strategies following appropriate risk assessment and counseling (see NCCN Guidelines for Breast Risk Reduction and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian). This process should involve multidisciplinary consultations prior to surgery, and should include a discussion of the risks associated with development of a contralateral breast cancer as compared with the risks associated with recurrent disease from the primary cancer. Except as specifically outlined in these guidelines, risk-reduction mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy is discouraged by the panel. The use of a prophylactic mastectomy contralateral to a breast treated with lumpectomy is very strongly discouraged in all patients.

The NCCN Panel recommends referring to the NCCN Guidelines for Older Adult Oncology for special considerations for this population.

Surgical Axillary Staging

The NCCN Guidelines for Breast Cancer include a section for surgical staging of the axilla for stages I, IIA, IIB, and IIIA (T3 N1 M0) breast cancer. Pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration (FNA)[157] or core biopsy must be considered in patients with clinically positive nodes to determine whether ALN dissection is needed.

Performance of SLN mapping and resection in the surgical staging of the clinically negative axilla is recommended and preferred by the panel for assessment of the pathologic status of the ALNs in patients with clinical stage I, stage II, and stage IIIA (T3 N1 M0) breast cancer.[55,158-166] This recommendation is supported by results of randomized clinical trials showing decreased arm and shoulder morbidity (ie, pain, lymphedema, sensory loss) in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard ALN dissection.[166,167] No significant differences in the effectiveness of the SLN procedure or level I and II dissection in determining the presence or absence of metastases in axillary nodes were seen in these studies.

However, not all women are candidates for SLN resection. An experienced SLN team is mandatory for the use of SLN mapping and excision.[168,169] Women who have clinical stage I or II disease and do not have immediate access to an experienced SLN team should be referred to an experienced SLN team for the definitive surgical treatment of the breast and surgical ALN staging. In addition, potential candidates for SLN mapping and excision should have clinically negative ALNs at the time of diagnosis, or a negative core or FNA biopsy of any clinically suspicious ALN(s). SLNs can be are assessed for the presence of metastases by both hematoxylin and eosin (H&E) staining and cytokeratin IHC. The clinical significance of a lymph node that is negative by H&E staining but positive by cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment decisions are based have relied on H&E staining, the panel does not recommend routine cytokeratin IHC to define node involvement and believes that current treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a randomized clinical trial (ACOSOG Z0010) for patients with H&E negative nodes where further examination by cytokeratin IHC was not associated with improved OS over a median of 6.3 years.[170] In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate. Multiple attempts have been made to identify cohorts of women with involved SLNs who have a low enough risk for non-SLN involvement that complete axillary dissection might be avoided if the SLN is positive. None of the early studies identified a low-risk group of patients with positive SLN biopsies but consistently negative non-sentinel nodes.[171-177] A randomized trial (ACOSOG Z0011) compared SLN resection alone with ALN dissection in women greater than or equal to 18 years of age with T1/T2 tumors, fewer than 3 positive SLNs, and undergoing breast-conserving surgery and whole breast irradiation. In this study, there was no difference in local recurrence, DFS, or OS between the two treatment groups. Only ER-negative status, age less than 50, and lack of adjuvant systemic therapy were associated with decreased OS.[178] At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of the ALN dissection group (n = 420) and 2.8% of the SLN dissection patients (n = 436) (*P* = .11). Median OS was approximately 92% in each group.[179] Therefore, based on these results after SLN mapping and excision, if a patient has a T1 or T2 tumor with 1 to 2 positive SLNs, did not receive preoperative systemic therapy, was treated with lumpectomy, and will receive whole breast radiation, the panel recommends no further axillary surgery.

The panel recommends level I and II axillary dissection when 1) patients have clinically positive nodes at the time of diagnosis that is confirmed by FNA or core biopsy; or 2) sentinel nodes are not identified. For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, the panel notes that axillary radiation may replace axillary dissection level I/II for regional control of disease.

Traditional level I and level II evaluation of ALN requires that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.[180,181] ALN should be extended to include level III nodes only if gross disease is apparent in the level II or III nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I and II).

Furthermore, according to the panel, without definitive data demonstrating superior survival with ALN dissection or SLN resection, these procedures may be considered optional in patients who have

particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, elderly patients, and patients with serious comorbid conditions. Women who do not undergo ALN dissection or ALN irradiation are at increased risk for ipsilateral lymph node recurrence.[182]

Radiation Therapy

Planning Techniques, Targets, and Doses

It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Whole Breast Radiation

Whole breast radiation reduces the risk of local recurrence and has shown to have a beneficial effect on survival.[136,139] Randomized trials have demonstrated decreased in-breast recurrences with an additional boost dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed.[183,184] The panel recommends whole breast irradiation to include breast tissue in its entirety. CT-based treatment planning is recommended to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the breast and lumpectomy site.

For greater homogeneity of target dose and to spare normal tissues using compensators such as tissue wedges, forward planning using segments, and IMRT may be used.[185,186] Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly heart and lung.[187] Radiation boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy.

Dose and Fractionation

Four randomized clinical trials have investigated hypofractionated whole breast radiation schedules (39–42.9 Gy in single fractions of 2.6–3.3 Gy) compared to standard 50 Gy in single fractions of 2 Gy.[188-191] The 10-year follow-up data from the START trials[192] are consistent with the 10-year results of the Canadian trial,[191] which reported that local tumor control and breast cosmesis were similar with a regimen of 42.5 Gy in 16 fractions over 3.2 weeks compared with 50 Gy in 25 fractions over 5 weeks.[191] The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated fraction regimen.[192] The NCCN Panel recommends whole breast irradiation, a dose of 46 to 50 Gy in 23 to 25 fractions, or a dose of 40 to 42.5 Gy in 15 to 16 fractions. Based on convenience and the data from the START trials,[192] the short course of radiation therapy (40–42.5 Gy in 15–16 fractions) is the NCCN-preferred option for treatment of patients receiving radiation therapy to the whole breast only. A boost to the tumor bed is recommended in patients with higher risk characteristics (such as age <50, high-grade disease, or patients with focally positive margins) in order to reduce local relapse.[69,71,184,192-194] Typical boost doses are 10 to 16 Gy in 4 to 8 fractions.

Chest Wall Radiation (Including Breast Reconstruction)

The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate. The NCCN Panel recommends a dose of 46 to 50 Gy in 23 to 25 fractions to the chest wall. A boost at the scar with a dose of 2 Gy per fraction to a total dose of approximately 60 Gy may be considered in some cases based on risk.

Regional Nodal Irradiation

The NCCN Guidelines include updated recommendations for regional lymph node irradiation in patients treated with lumpectomy and mastectomy depending on lymph node involvement (see *Principles of Radiation Therapy* in the NCCN Guidelines for Breast Cancer).

Two studies, MA.20 and EORTC 22922/10925, evaluated the addition of regional nodal irradiation to the internal mammary nodes and the upper axillary nodes including the supraclavicular region, in addition to whole breast irradiation or chest wall irradiation after lumpectomy or mastectomy, respectively. In MA.20, regional recurrences were reduced from 2.7% with breast irradiation only to 0.7% with the addition of nodal irradiation.[195] The distant recurrences were reduced from 17.3% to 13.4%.[195] An improvement in DFS was seen from 77% to 82% at 10 years in those who received regional nodal irradiation compared to those who did not.[195] In EORTC 22922/10925, regional radiation therapy reduced the incidence of regional recurrences from 4.2% to 2.7% and decreased the rate of distant metastases from 19.6% to 15.9% at a median follow-up of 10.9 years.[196]

Accelerated Partial Breast Irradiation

Several studies have been reported using accelerated partial breast irradiation (APBI) rather than whole breast irradiation following complete surgical excision of in-breast disease. The panel generally views the use of APBI as investigational, and encourages its use within the confines of a high-quality, prospective clinical trial.[197] For patients who are not trial eligible, recommendations from ASTRO indicate that APBI may be suitable in selected patients with early-stage breast cancer and may be comparable to treatment with standard whole-breast RT.[198] Patients who may be suitable for APBI are women 60 years of age and older who are not carriers of a known *BRCA1/2* mutation and who have been treated with primary surgery for a unifocal stage I, ER-positive cancer. Tumors should be infiltrating ductal or have a favorable histology, should not be associated with an extensive intraductal component or LCIS, and should have negative margins. Thirty-four Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy to the tumor bed is recommended. Other fractionation schemes are under investigation. Studies have suggested that the ASTRO stratification guidelines may not adequately predict ipsilateral breast tumor recurrences following APBI.[199,200] Follow-up is limited and studies are ongoing.

Radiation Therapy in Patients Receiving Preoperative Systemic Therapy

The panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative systemic chemotherapy should be made based on maximal stage from pre-chemotherapy tumor characteristics and/or pathological stage, irrespective of tumor response to preoperative systemic therapy.

Radiation Therapy After Lumpectomy

After lumpectomy, whole breast irradiation is strongly recommended with or without boost to tumor bed for node-positive disease (category 1 for those with positive nodes; category 2A for those with negative axillary nodes). This recommendation is supported by the results of a

meta-analysis by the EBCTCG showing reduction in 10-year risk of recurrence in those who received whole breast irradiation versus those who did not (19% vs. 35%; RR 0.52; 95% CI, 0.48–0.56).[139] In addition, a significant reduction in 15-year risk of breast cancer death (21% vs. 25%; RR 0.82; 95% CI, 0.75–0.90) was also observed.[139]

Regional Nodal Irradiation

The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the MA.20 and EORTC 22922/10925 trials support the importance of regional nodal irradiation after lumpectomy.[195,196] The NCCN Panel strongly recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥4 positive nodes). Irradiation of the regional nodal area is generally not recommended by the panel for those with negative axillary nodes.

If adjuvant chemotherapy is indicated after lumpectomy, radiation should be given after chemotherapy is completed.[201,202] This recommendation is based on results of the "Upfront-Outback" trial in which patients who had undergone breast-conserving surgery and axillary dissection were randomly assigned to receive chemotherapy following radiation therapy or radiation therapy following chemotherapy. The initial results showed an increased rate of local recurrence in the group with delayed radiotherapy at a median follow-up of 58 months;[202] however, differences in rates of distant or local recurrence were not statistically significant when the two arms were compared at 135-month follow-up.[201]

Radiation Therapy After Lumpectomy in Older Adults

Whole breast irradiation as a component of breast-conserving therapy is not always necessary in selected women 70 years of age or older. In a study of women with clinical stage I, ER-positive breast cancer who were greater than or equal to 70 years of age at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for five years. Locoregional recurrence rates were 1% in the lumpectomy, radiation, and tamoxifen arm and 4% in the lumpectomy plus tamoxifen arm. There were no differences in OS, DFS, or need for mastectomy.[203] These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.[204] At 10 years, a statistically significant reduction in ipsilateral breast recurrences was seen with radiation therapy with 90% of patients in the lumpectomy and tamoxifen arm compared with 98% in the lumpectomy plus radiation and tamoxifen arm who were free from locoregional recurrence.[204] Similar results were obtained in other studies of similar design.[205,206] Whether the difference in tumor control is clinically significant and the patient receives breast radiotherapy should be individualized based upon discussion between the patient and her care team.

The NCCN Guidelines allow for the use of lumpectomy (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women greater than or equal to 70 years of age with clinically negative lymph nodes and ER-positive, T1 breast cancer (category 1).

Radiation Therapy After Mastectomy

Node-Positive Disease: Randomized clinical trials have shown that a DFS and OS advantage is conferred by the irradiation of chest wall and regional lymph nodes in women with positive ALNs after mastectomy and ALN dissection.[207-211] In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results of EBCTCG meta-analyses[212] show that radiotherapy after mastectomy and axillary node dissection reduced both recurrence and breast cancer mortality in the women with 1 to 3 positive lymph nodes even when

systemic therapy was administered.[196] Based on these studies, the current guidelines recommend postmastectomy chest wall irradiation in women with positive ALNs (category 1). Two retrospective analyses have provided evidence for benefit of radiation therapy for only selected patients (patients presenting with clinical stage III disease and patients with four or more positive nodes) receiving preoperative systemic therapy prior to mastectomy.[213,214]

Regional Nodal Irradiation

The use of regional nodal irradiation for patients undergoing mastectomy is supported by a subgroup analysis of studies from the Danish Breast Cancer Cooperative Group.[215] In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive ALNs. In addition, data from the EORTC 22922/10925 trial supports the role of regional RT in this population based on the inclusion of patients who had undergone mastectomy in this study. Based on the above data, the NCCN Panel recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥4 positive nodes; 2A for 1–3 positive nodes).

Node-Negative Disease: Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm or positive pathologic margins. Chest wall irradiation is recommended for these patients.[216] Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes, especially in patients with tumors greater than 5 cm, or positive surgical margins. In patients with tumors less than or equal to 5 cm and negative margins but less than or equal to 1 mm, chest wall irradiation should be considered.

In patients with negative nodes, tumor less than or equal to 5 cm, and clear margins (≥1 mm), post-mastectomy radiation therapy is usually not recommended. However, the panel has noted that it may be considered only for patients with high risk of recurrence. A retrospective analysis suggests benefit of post-mastectomy radiation therapy in reducing risk of recurrence in patients with node-negative disease with high-risk factors such as close margins, tumors greater than or equal to 2 cm, premenopausal status, and lymphovascular invasion.[217] Another study showed increased risk of locoregional recurrence in women with node-negative triple-negative breast cancer with tumors less than or equal to 5 cm.[218]

Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation and be offered an opportunity to consult with a reconstructive plastic surgeon. Breast reconstruction should not interfere with the appropriate surgical management. This may increase the risk of overall and cancer-related death, especially in those with late-stage disease.[219] Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable timeframe.

Several reconstructive approaches are summarized for these patients in the NCCN Guidelines for Breast Cancer under *Principles of Breast Reconstruction Following Surgery*.

The decision regarding type of reconstruction includes patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. Smoking and obesity increase the risk of complications for all types of

breast reconstruction whether with implant or flap.[220-224] Smoking and obesity are therefore considered a relative contraindication to breast reconstruction by the NCCN Panel. Patients should be informed of increased rates of wound healing complications and partial or complete flap failure among smokers and obese patients.

Reconstruction is an optional procedure that does not impact the probability of recurrence or death, but it is associated with an improved quality of life for many patients. It is sometimes necessary to perform surgery on the contralateral breast (ie, breast reduction, implantation) to achieve optimal symmetry between the ipsilateral reconstructed breast and the contralateral breast.

Breast Reconstruction After Mastectomy

Mastectomy results in loss of the breast for breastfeeding, loss of sensation in the skin of the breast and nipple-areolar complex (NAC), and loss of the breast for cosmetic, body image, and psychosocial purposes. The loss of the breast for cosmetic, body image, and psychosocial issues may be partially overcome through the performance of breast reconstruction with or without reconstruction of the NAC.

Women undergoing mastectomy should be offered consultation regarding options and timing of breast reconstruction.

Many factors must be considered in the decision-making about breast reconstruction. There are several different types of breast reconstruction that include the use of implants, autogenous tissues, or both.[225-227] Reconstruction with implants can be performed either by immediate placement of a permanent subpectoral implant or initial placement of a subpectoral expander implant followed by gradual expansion of the implant envelope with stretching of the pectoralis major muscle and overlying skin followed by replacement of the expander with a permanent implant. A wide variety of implants are available that contain saline, silicone gel, or a combination of saline and silicone gel inside a solid silicone envelope.

Autogenous tissue methods of reconstruction use various combinations of fat, muscle, skin, and vasculature from donor sites (ie, abdomen, buttock, back) that may be brought to the chest wall with their original blood supply (pedicle flap) or as free flaps with microvascular anastomoses to supply blood from the chest wall/thorax.[228] Several procedures using autologous tissue are available including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction.

Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications following autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Reconstruction can be performed either at the time of the mastectomy known as “immediate breast reconstruction” and under the same anesthetic or in a delayed fashion any time, known as “delayed breast reconstruction.” In many cases, breast reconstruction involves a staged approach requiring more than one procedure such as surgery on the contralateral breast to improve symmetry, revision surgery involving the breast and/or donor site, and/or nipple and areola reconstruction and tattoo pigmentation.

Plans for post-mastectomy radiation therapy can impact decisions related to breast reconstruction since there is a significantly increased

risk of implant capsular contracture following irradiation of an implant. Furthermore, postmastectomy irradiation may have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction, and may interfere with the targeted delivery of radiation when immediate reconstruction is performed using either autologous tissue or breast implants.[229,230] Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.[231] The preferred approach to breast reconstruction for irradiated patients was a subject of controversy among the panel. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, generally radiation therapy is preferred to precede autologous reconstruction due to the reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is planned in a post mastectomy patient requiring radiation therapy, the NCCN Panel prefers a staged approach with immediate tissue expander placement followed by implant placement. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy.

In a previously radiated patient, the use of tissue expanders/implants is relatively contraindicated.[232] Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.[233,234] If a patient has previously received radiation therapy to the breast, autologous tissue reconstruction is the preferred method of breast reconstruction.

Skin-sparing Mastectomy

Skin-sparing mastectomy procedures are appropriate for some patients and involve removal of the breast parenchyma including the NAC while preserving the majority of the original skin envelope, and are followed by immediate reconstruction with autogenous tissue, a prosthetic implant, or a composite of autogenous tissue and an implant.

Skin-sparing mastectomy involving preservation of the skin of the NAC has become the subject of increased attention. Possible advantages of this procedure include improvements in breast cosmesis, body image, and nipple sensation following mastectomy, although the impact of this procedure on these quality-of-life issues has not been well-studied.[235-237] There are limited data from surgical series, with short follow-up, that suggest that performance of NAC-sparing mastectomy in selected patients is associated with low rates of occult involvement of the NAC with breast cancer and local disease recurrence.[236,238,239] NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. According to the NCCN Panel, when considering a NAC-sparing procedure, assessment of nipple margins is mandatory. Retrospective data support the use of NAC-sparing procedures for patients with breast cancer with low rates of nipple involvement and low rates of local recurrence due to early-stage, biologically favorable (ie, Nottingham grade I or 2, node-negative, HER2-negative, no lymphovascular invasion) invasive cancers and/or DCIS that are peripherally located in the breast (>2 cm from nipple).[240,241] Contraindications for nipple preservation include evidence of nipple involvement such as Paget's disease or other nipple discharge associated with malignancy and/or imaging findings suggesting malignant involvement of nipple and subareolar tissues. Several prospective trials are underway to evaluate NAC-sparing mastectomy in the setting of cancer and enrollment in such trials is encouraged.

Advantages of a skin-sparing mastectomy procedure include an improved cosmetic outcome resulting in a reduction in the size of the mastectomy scar and a more natural breast shape, especially when autologous tissue is used in reconstruction,[242] and the ability to perform immediate reconstruction. Although no randomized studies have been performed, results of several mostly retrospective studies have indicated that the risk of local recurrence is not increased when patients receiving skin-sparing mastectomies are compared with those undergoing non-skin–sparing procedures. However, strong selection biases almost certainly exist in the identification of patients appropriate for skin-sparing procedures.[243-247] Reconstruction of the NAC may also be performed in a delayed fashion if desired by the patient. Reconstructed nipples are devoid of sensation. According to the NCCN Panel, skin-sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin-sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied for patients treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

Breast Reconstruction After Lumpectomy

Issues related to breast reconstruction also pertain to women who undergo or have undergone a lumpectomy, particularly in situations where the surgical defect is large and/or expected to be cosmetically unsatisfactory. An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection by itself would likely yield an unacceptable cosmetic outcome.[248] The evolving field of oncoplastic surgery includes the use of “volume displacement” techniques performed in conjunction with a large partial mastectomy.[249] Oncoplastic volume displacement procedures combine the removal of generous regions of breast tissue (typically designed to conform to the segmentally distributed cancer in the breast) with “mastopexy” techniques in which remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect and thereby avoid the creation of significant breast deformity. Volume displacement techniques are generally performed during the same operative setting as the breast-conserving lumpectomy by the same surgeon who is performing the cancer resection.[249,250]

Advantages of oncoplastic volume displacement techniques are that they permit the removal of larger regions of breast tissue, thereby achieving wider surgical margins around the cancer, and at the same time better preserve the natural shape and appearance of the breast than do standard breast resections.[251]

Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the United States, and the possible necessity for subsequent mastectomy if pathologic margins are positive when further breast-conserving attempts are deemed impractical or unrealistic. Nevertheless, the consensus of the panel is that these issues should be considered prior to surgery for women who are likely to have a surgical defect that is cosmetically unsatisfactory, and that women who undergo lumpectomy and are dissatisfied with the cosmetic outcome after treatment should be offered a consultation with a plastic surgeon to address the repair of resulting breast defects. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include re-excision segmental resection, or could require mastectomy with or without loss of the

nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

Finally, decisions regarding breast reconstruction should primarily focus on treatment of the tumor, and such treatment should not be compromised.

Systemic Therapies (Preoperative and Adjuvant)

Principles of Preoperative Systemic Therapy

The NCCN Panel has outlined the rationale, appropriate patient selection, and response assessment for preoperative systemic therapy in a new section titled, *Principles of Preoperative Chemotherapy*.

Rationale for Preoperative Chemotherapy

Randomized clinical trials have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery.[252,253] Historically, a primary advantage of administering preoperative systemic therapy has been to improve surgical outcomes. Preoperative systemic therapy can render inoperable tumors resectable and also downstage patients with operable breast cancer desiring breast conservation.[254] Results from large clinical trials and retrospective reviews indicate that breast conservation rates are improved with preoperative systemic therapy.[253,255] Clinicians need to carefully consider the extent of disease in the breast and likelihood of adequate tumor response before recommending preoperative systemic therapy to improve the likelihood of successful breast conservation.

In addition, use of preoperative systemic therapy may provide important prognostic information based on response to therapy. Achieving a pathologic complete response (pCR) to neoadjuvant therapy is associated with favorable disease-free and OS in early-stage breast cancer. The correlation between pathologic response and long-term outcomes in patients with early-stage breast cancer is strongest for patients with triple-negative breast cancer, less so for HER2-positive disease, and least for hormone-positive disease.[256-258]

Other benefits of preoperative systemic therapy include allowing time for appropriate genetic testing and for planning breast reconstruction in patients proceeding with mastectomy. For those with significant residual disease after standard preoperative systemic therapy, it may provide an opportunity to identify patients who are candidates for clinical trials of novel agents in the adjuvant setting. To date, the tailoring of therapy based on poor response to standard preoperative chemotherapy has not yet demonstrated improved outcomes. In addition, preoperative systemic therapy also serves as an excellent research platform to test novel therapies and predictive biomarkers by providing tumor specimens and blood samples prior to and during systemic treatment.

Selection of Patients for Preoperative Therapy

Not all patients are appropriate candidates for preoperative systemic therapy. According to the NCCN Panel, among those with inoperable breast tumors, preoperative systemic therapy is indicated in women with locally advanced or inoperable breast cancer including those with inflammatory breast cancer; those with N2 and N3 regional lymph node nodal disease; and T4 tumors. In patients with operable breast cancer who are clear candidates for adjuvant chemotherapy, preoperative systemic therapy may be considered if a patient desires breast-conserving surgery but the surgery is not possible due to the size of the tumor relative to that of the breast, with the hope that this will help obtain clear surgical margins at final resection. Preoperative systemic therapy may also be administered in patients with operable tumors if the patient's breast cancer subtype is one associated with a high likelihood of response. When preoperative systemic therapy is used to improve

the likelihood of successful breast conservation, the surgical plan should consider the possibility that clear surgical margins may not always be obtained, and a follow-up mastectomy may be required, with or without breast reconstruction. This consideration is especially important when oncoplastic breast reduction techniques or contralateral breast symmetry procedures are added to the breast-conserving surgery to achieve optimal cosmetic outcomes.

The NCCN Panel cautions that preoperative systemic therapy is not appropriate for certain patients. Preoperative systemic therapy should not be offered in patients with extensive in situ disease when the extent of invasive disease cannot be defined; in patients where the extent of the tumor is poorly delineated; or in those whose tumors are not palpable or clinically assessable. The decision to utilize preoperative therapy should be made in the context of a coordinated and collaborative multi-disciplinary team.

Preoperative Systemic Therapy Options
Chemotherapy: A number of chemotherapy regimens have activity in the preoperative setting. According to the NCCN Panel, those regimens recommended in the adjuvant setting may be considered in the preoperative setting. In both settings, the underlying aim remains the same: eradication or control of undiscovered distant metastases.

Endocrine Therapy: Neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor-positive tumors.[259-266] According to the NCCN Panel, the endocrine therapy options include an aromatase inhibitor (with ovarian suppression for premenopausal women) or tamoxifen. The preferred endocrine therapy option for postmenopausal women is an aromatase inhibitor.

HER2 Targeted Therapy: For patients with HER2-positive breast cancer, that are candidates for preoperative systemic therapy, chemotherapy and trastuzumab-based therapy is recommended.[267] Chemotherapy and dual anti-HER2 blockade associated with trastuzumab plus pertuzumab has shown significant improvements in the pCR rate when compared with chemotherapy and one anti-HER2 agent in the preoperative setting.[268-270] In the Neosphere trial, the addition of pertuzumab to trastuzumab and docetaxel preoperatively led to a statistically significant increase in pCR in the breast (16.8% increase; 95% CI, 3.5–30.1; *P* = .0141).[270] In the TRYPHAENA trial, preoperative therapy with pertuzumab and trastuzumab given along with anthracycline-containing or anthracycline-free standard chemotherapy regimens to patients with operable, locally advanced, or inflammatory HER2-positive breast cancer showed pCR rates in all treatment arms ranging from 57% to 66%.[271] The mean change in left ventricular ejection fraction was similar in all treatment arms.[271] The NCCN Panel supports the FDA-approved indication that a pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2, or greater than or equal to N1, HER2-positive, early-stage breast cancer.

Response Assessment During Preoperative Chemotherapy: The NCCN panel recommends that tumor response should be routinely assessed by clinical exam during the delivery of preoperative systemic therapy. Patients with operable breast cancer experiencing progression of disease while undergoing preoperative systemic therapy should be taken promptly to surgery. Imaging during preoperative systemic therapy should not be done routinely, but may be considered if tumor progression is suspected. Imaging prior to surgery should be determined by a multi-disciplinary team

Systemic Adjuvant Therapy

After surgical treatment, adjuvant systemic therapy should be considered. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/PR and HER2 status).

The published results of the EBCTCG overview analyses of adjuvant chemotherapy and tamoxifen show convincing reductions in the odds of recurrence and death in all age groups for chemotherapy and endocrine therapy.[4,272] Thus, the current guidelines recommend adjuvant therapy without regard to patient age (category 1). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy, and comorbidity.[273,274] The decision-making process requires collaboration between the health care team and patient.

Estimating Risk of Relapse or Death and Benefits of Systemic Treatment

Several prognostic factors predict for future recurrence or death from breast cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved ALNs, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,[273] and a validated, computer-based model (Adjuvant! Online; www.adjuvantonline.com) is available to estimate 10-year DFS and OS that incorporates all of the above prognostic factors except for HER2 tumor status.[274,275] These tools aid the clinician in objectively estimating outcome with local treatment only, and also assist in estimating the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. These estimates may be utilized by the clinician and patient in their shared decision-making regarding the toxicities and benefits of systemic adjuvant therapy.[276]

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer.[277] More importantly, HER2 tumor status also provides predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in the selection of therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have demonstrated that anthracycline-based adjuvant therapy is superior to non-anthracycline–based adjuvant chemotherapy in patients with HER2-positive tumors,[278-282] and that the dose of doxorubicin may be important in the treatment of tumors that are HER2-positive.[283] Prospective evidence of the predictive utility of HER2 status in early-stage [284-289] and metastatic breast cancer[290-292] is available for trastuzumab-containing therapies.

Use of DNA microarray technologies to characterize breast cancer has allowed for development of classification systems of breast cancer by gene expression profile.[293] Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (luminal A and luminal B subtypes); ER-negative/HER2-negative (basal subtype); HER2-positive; and tumors that have characteristics similar to normal breast tissue.[294-296] In retrospective analyses, these gene expression subtypes are associated with differing relapse-free survival and OS.

There are many gene-based assays to predict prognosis such as distant recurrence, local recurrence, or survival.

The 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue is among the best-validated prognostic assays, and there

are data showing that it can predict who is most likely to respond to systemic chemotherapy.

Studies have shown that the 21-gene assay recurrence score obtained is predictive of locoregional and distant recurrence for postmenopausal women treated with tamoxifen or those treated with an aromatase inhibitor.[297-299] Studies have also demonstrated the ability of the recurrence score to independently predict response to adjuvant chemotherapy.[300-302] Unplanned, retrospective subset analysis from a single randomized clinical trial in post-menopausal, ALN-positive, ER-positive breast cancer found that the 21-gene RT-PCR assay may provide predictive information for chemotherapy benefit in addition to tamoxifen.[300] Patients with a high score in the study benefited from chemotherapy, whereas patients with a low score did not appear to benefit from the addition of chemotherapy regardless of the number of positive lymph nodes.[300] Many other multi-gene or multi-gene expression assay systems have been developed.

The 70-gene signature assay uses microarray technology to analyze gene expression profile from breast tumor tissue (formalin-fixed, paraffin-embedded fresh or frozen breast tumor tissue) to help identify patients with early-stage breast cancer likely to develop distant metastases.[303-309] This assay is approved by the FDA to assist in assignment of women with ER-positive or ER-negative breast cancer into a high versus low risk for recurrence, but not for predicting benefit from adjuvant systemic therapy. The prospective RASTER study reported that breast cancer patients classified by the 70-gene signature as low risk (of whom 85% did not receive adjuvant chemotherapy) had an overall 97% distant recurrence-free interval at five years.[310]

Another assay with 50 genes identifies intrinsic breast cancer subtypes (luminal A, luminal B, HER2 enriched and basal-like) in addition to generating a risk of recurrence (ROR) score that can be used to predict prognosis among postmenopausal women with hormone-positive breast cancer. In a retrospective analysis of the ATAC trial,[311] the ROR score obtained using the 50-gene assay in postmenopausal patients treated with adjuvant tamoxifen or anastrozole was seen to have a continuous relationship with the risk of distant recurrence at 10 years in node-negative *and* node-positive disease. The retrospective analysis also compared the ROR score obtained using the 50-gene assay with the recurrence score obtained using the 21-gene assay. Both assays identified similar percentage of low-risk patients (hormone receptor-positive, node-negative) with similar risk of recurrence. The ABCSG-8 trial showed that the ROR score provides prognostic information and predicts the risk of distant recurrence in postmenopausal women with ER-positive early-stage breast cancer.[312] A recent combined analysis of the ATAC and the ABCSG-8 trials reported ROR score as a strong predictor of late distant recurrence (greater than 5 years) for patients with hormone receptor-positive, node-negative disease.[313]The NCCN Panel members acknowledge that many assays have been clinically validated for prediction of prognosis. However, based on the currently available data, the panel believes that the 21-gene assay has been best validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy.

Patients with a high recurrence score obtained using the 21-gene assay clearly benefit from chemotherapy, whereas patients with a low score do not appear to benefit from the addition of chemotherapy regardless of the number of positive lymph nodes.[300] The results from the prospective TAILORx study support the use of the 21-gene assay to spare the use of chemotherapy in patients with a low-risk score.[314] In patients with a low-risk score (≤10) at 5 years, the risk of the recurrence

of breast cancer at a distant site was less than 1% and the risk of any recurrence was less than 2%.[314]

The additional benefit from adjuvant chemotherapy in addition to endocrine therapy is currently unclear for patients with intermediate recurrence score. The long-term follow-up results from the TAILORx trial clarify the use of chemotherapy in women with hormone-receptor–positive, HER2-negative, axillary node–negative invasive breast cancer with mid-range 21-gene assay recurrence score (between 11–25).[315] The ongoing RxPONDER trial is evaluating whether adjuvant chemotherapy is beneficial in patients with hormone receptor-positive, HER2-negative breast cancer with positive ALNs and a recurrence score of 25 or less.[316]

The MINDACT trial is phase III trial comparing the 70-gene signature with the commonly used clinicopathologic criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes.[317] The early results from the MINDACT trial suggest that the 70-gene signature can help avoid chemotherapy in certain patients regardless of larger tumor size and nodal status, without compromising the outcome.[318] Among the MINDACT trial patients, if decision on administering adjuvant chemotherapy was based on clinical characteristics alone (tumor size and nodal status), 50% would receive adjuvant chemotherapy; however, only 36% received chemotherapy using the risk status based on the 70-gene signature—an absolute reduction of 14% in chemotherapy administration rate.[318]

Axillary Lymph Node-Negative Tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal incremental benefit and is not recommended as treatment of the invasive breast cancer. According to the NCCN Panel, endocrine therapy may be considered to reduce the risk for a second contralateral breast cancer, especially in those with ER-positive disease. The NSABP database demonstrated a correlation between the ER status of a new contralateral breast tumor and the original primary tumor, which reinforced the notion that endocrine therapy is not an effective strategy to reduce the risk for contralateral breast cancer in patients diagnosed with ER-negative tumors.[319]

Patients with invasive ductal or lobular tumors greater than 0.5 cm in diameter and no lymph node involvement may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features that warrant consideration of adjuvant therapy. Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade, high histologic grade, HER2-positive status, or hormone receptor-negative status. The use of endocrine therapy and chemotherapy in these relatively lower risk subsets of women must be based on balancing the expected absolute risk reduction and the individual patient's willingness to experience toxicity to achieve that incremental risk reduction.

For women with lymph node-negative, hormone receptor-*negative* tumors less than or equal to 0.5 cm with micrometastasis (pN1mi) or tumors 0.6 to 1.0 cm, the NCCN Guidelines suggest considering adjuvant chemotherapy (category 2A). For tumors greater than 1 cm in diameter chemotherapy is a category 1 recommendation.

For those with lymph node-negative, hormone receptor-positive breast cancer tumors greater than 0.5 cm, the panel recommends endocrine therapy (category 1) with the consideration of chemotherapy. Incremental benefit of combination chemotherapy in patients with lymph node-negative, hormone receptor-positive breast cancer may be

relatively small.[320] However, chemotherapy should not be withheld from these patients solely based on ER-positive tumor status.[4,320,321] The panel considers the 21-gene RT-PCR assay an option for these patients to help estimate likelihood of recurrence *and* benefit from chemotherapy. The panel emphasizes that the recurrence score should be used for decision-making only in the context of other elements of risk stratification for an individual patient.

Axillary Lymph Node-Positive Tumors

Patients with lymph node-positive disease are most often candidates for chemotherapy and, if the tumor is hormone receptor-positive, for the addition of endocrine therapy (category 1). When HER2 is amplified or over-expressed, HER2-targeted therapy should be incorporated into the adjuvant chemotherapy. The NCCN Panel has noted in a footnote that the 21-gene RT-PCR assay recurrence score can be considered in select patients with 1 to 3 involved ipsilateral ALNs to guide the addition of combination chemotherapy to standard hormone therapy based on the retrospective study by Albain et al.[300]

Stratification for Systemic Adjuvant Therapy

The NCCN Guidelines stratify patients with breast cancer based on their hormone receptor status and HER2 expression. Patients are then further stratified based on risk of disease recurrence based on anatomic and pathologic characteristics (ie, tumor grade, tumor size, ALN status, angiolymphatic invasion).

Adjuvant Endocrine Therapy

The NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers.[17] Patients with invasive breast cancers that are ER or PR positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered.[322] Selected studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this finding.[280,323-330] A retrospective analysis of tumor blocks collected in the ATAC trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.[331] However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends the use of adjuvant endocrine therapy in the majority of women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor.

Tamoxifen

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.[4] In women with ER-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or ALN status.[4] In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[321] Prospective randomized trials have demonstrated that 5 years of tamoxifen is more effective than 1 to 2 years of tamoxifen.[332,333]

The ATLAS trial randomly allocated 12,894 women to continue tamoxifen up to 10 years or to discontinue tamoxifen (control). The outcome analyses of 6846 women with ER-positive disease showed that by extending adjuvant treatment to 10 years, the risk of relapse and breast cancer-related mortality was reduced.[334] The risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction 3.7%). Patients receiving tamoxifen beyond 10 years of treatment had a greater reduction in risk of progression, possibly due to a “carryover effect.” The

reduction in risk of recurrence was 0.90 (95% CI, 0.79–1.02) during 5 to 9 years of tamoxifen treatment and 0.75 (0.62–0.90) after 10 years of treatment. Furthermore, reduced mortality was apparent after completion of 10 years of treatment with tamoxifen. With regards to toxicity, the most important adverse effects noted in all women in the ATLAS trial after treatment with 10 years of tamoxifen were an increased risk for endometrial cancer and pulmonary embolism. The recurrence rate ratio reported for pulmonary embolus was 1.87 (95% CI, 1.13–3.07; *P* = .01 [including 0.2% mortality in both groups]) and for endometrial cancer was 1.74 (1.30–2.34, *P* = .0002). The cumulative risk for endometrial cancers during 5 to 14 years was 3.1%, with a mortality of 0.4% associated with endometrial cancer, higher than what was noted in the control group of patients receiving only 5 years of therapy (cumulative risk: 1.6%; mortality: 0.2%).[334] The results of the aTTom trial confirm the ATLAS reduction in recurrence and death from breast cancer.[335]

In women who are premenopausal at diagnosis, the NCCN Panel recommends tamoxifen treatment with or without ovarian suppression/ablation. Ovarian ablation may be accomplished by surgical oophorectomy or by ovarian irradiation. Ovarian suppression utilizes luteinizing hormone-releasing hormone (LHRH) agonists that result in suppression of luteinizing hormone (LH) and release of follicle-stimulating hormone (FSH) from the pituitary and reduction in ovarian estrogen production. Available LHRH agonists in the United States include goserelin and leuprolide and, when used for ovarian suppression, both agents should be given as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients.

The EBCTCG performed a meta-analysis of randomized studies of ovarian ablation or suppression alone versus no additional systemic adjuvant therapy for early-stage breast cancer. Analysis of ovarian suppression versus no adjuvant therapy did not demonstrate significant reduction in recurrence (HR 0.72; 95% CI, 0.49–1.04) or death (HR 0.82; 95% CI, 0.47–1.43).[336] In addition, data on ovarian suppression with tamoxifen, chemotherapy, or both showed no significant reduction in reduced recurrence or death.

Studies in premenopausal women of ovarian ablation or suppression alone versus CMF (cyclophosphamide/methotrexate/fluorouracil) chemotherapy alone generally demonstrate similar antitumor efficacy in patients with hormone receptor-positive tumors and superior outcomes with CMF in patients with hormone receptor-negative tumors.[336-344] There is also the suggestion that the benefits of ovarian suppression/ablation may be greater in the younger premenopausal group. Studies in premenopausal women of ovarian ablation/suppression plus tamoxifen versus chemotherapy alone generally demonstrate no difference in rates of recurrence or survival.[345-347]

A large intergroup study in premenopausal women with hormone receptor-positive, node-positive breast cancer studied adjuvant CAF (cyclophosphamide/doxorubicin/5-fluorouracil) chemotherapy versus CAF plus ovarian suppression with goserelin (CAF-Z) versus CAF-Z plus tamoxifen (CAF-ZT).[337] The results demonstrated no improvement in time to recurrence or OS comparing CAF with CAF-Z. There was improvement in time to recurrence (HR, 0.73; 95% CI, 0.59–0.90; *P* < .01) but not OS with CAF-Z compared with CAF-ZT (HR, 0.91; 95% CI, 0.71–1.15; *P* = .21). This study did not include a CAF plus tamoxifen arm, so the contribution of the goserelin to the improved time to recurrence in the CAF-ZT arm cannot be assessed. The addition of ovarian suppression/ablation has also been subjected to meta-analysis by the EBCTCG.[345] They identified no statistically significant reduction in annual rates of recurrence or death with the addition of ovarian

suppression or ablation to chemotherapy in women less than 40 years or 40 to 49 years of age.

Recent data from the randomized TEXT–SOFT trials evaluating adjuvant endocrine therapy show that the aromatase inhibitor exemestane plus ovarian suppression significantly reduces recurrences as compared with tamoxifen plus ovarian suppression.

In two randomized trials (TEXT and SOFT), premenopausal women with hormone receptor-positive early-stage breast cancer were assigned to receive exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years.[348] Suppression of ovarian estrogen production was achieved with the use of the gonadotropin-releasing hormone agonist triptorelin, oophorectomy, or ovarian irradiation. The DFS was 92.8% in the exemestane plus ovarian suppression group, as compared with 88.8% in the tamoxifen plus ovarian suppression group (HR for recurrence, 0.66; 95% CI, 0.55–0.80; $P < .001$).[348] The OS did not differ significantly between the two groups (HR for death in the exemestane plus ovarian suppression group, 1.14; 95% CI, 0.86–1.51; $P = .37$).[348] In the SOFT trial,[349] premenopausal women with hormone-receptor breast cancer were randomized to tamoxifen alone, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression for 5 years. In the primary analysis, tamoxifen plus ovarian suppression was not superior to tamoxifen alone for DFS. After 67 months of median follow-up, the DFS rate at 5 years was 86.6% in the tamoxifen–ovarian suppression group and 84.7% in the tamoxifen alone group (HR 0.83; 95% CI, 0.66–1.04; $P = .10$).[349] In a subgroup analysis, women at high risk of recurrence, who received prior chemotherapy, had improved outcomes with ovarian suppression. Their chance of remaining disease-free at 5 years was 78% with tamoxifen alone, 82.5% with tamoxifen and ovarian suppression, and 85.7% with exemestane and ovarian suppression.[349] In the subgroup of women with no prior chemotherapy, no meaningful benefit was seen from ovarian suppression, as women who received tamoxifen alone demonstrated a 95% chance of remaining disease-free for 5 years.[349] The OS data from these trials is still pending because the overall follow-up is relatively short in the context of endocrine-sensitive disease.

Based on the results of the SOFT and TEXT trials, the NCCN Panel has included ovarian suppression plus an aromatase inhibitor for 5 years as an adjuvant endocrine therapy option for premenopausal women with hormone-receptor–positive breast cancer at higher risk of recurrence (eg, young age, high-grade tumor, lymph-node involvement).

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2 to 3 years of tamoxifen, or as extended therapy following 4.5 to 6 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot reliably be assessed owing to treatment-induced amenorrhea. The results from two prospective, randomized, clinical trials have provided evidence of an OS benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole (HR, 0.53; 95% CI, 0.28–0.99; $P = .045$) or exemestane (HR, 0.83; 95% CI, 0.69–1.00; $P = .05$ [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.[350,351] In addition, the NCIC-CTG MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with ALN-positive (but not lymph node-negative), ER-positive breast cancer.[352] However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor

versus first-line tamoxifen.[353,354] Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes and night sweats and may cause vaginal dryness. Aromatase inhibitors are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, while tamoxifen is associated with an increased risk for uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an aromatase inhibitor. The ATAC trial demonstrated that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor-positive breast cancer.[355,356] With a median of 100 months follow-up, results in 5216 postmenopausal women with hormone receptor-positive, early-stage breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for DFS, 0.85; 95% CI, 0.76–0.94; *P* = .003) with anastrozole compared with tamoxifen.[353] No difference in survival has been observed (HR, 0.90; 95% CI, 0.75–1.07; *P* = .2). Patients in the combined tamoxifen and anastrozole group gained no benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near complete elimination of endogenous estrogen levels.[356] ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue;[357] similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that overall quality of life was not significantly impaired;[358] a greater loss of bone mineral density with anastrozole;[359] a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance;[360] and no evidence for an interaction between prior chemotherapy and anastrozole.[361]

BIG 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first 2 years of treatment only.[354] With 8010 women included in the analysis, DFS was superior in the letrozole-treated women (HR, 0.81; 95% CI, 0.70–0.93; log rank *P* = .003). No interaction between PR expression and benefit was observed. No difference in OS was observed. A comparison of the cardiovascular side effects in the tamoxifen and letrozole arms of the BIG 1-98 trial showed that the overall incidence of cardiac adverse events was similar (letrozole, 4.8%; tamoxifen, 4.7%). However, the incidence of grade 3 to 5 cardiac adverse events was significantly higher in the letrozole arm, and both the overall incidence and incidence of grade 3 to 5 thromboembolic events was significantly higher in the tamoxifen arm.[362] In addition, a higher incidence of bone fracture was observed for women in the letrozole arm compared with those in the tamoxifen arm (9.5% vs. 6.5%).[363] After a longer follow-up (median 71 months) no significant improvement in DFS was noted with either tamoxifen followed by letrozole or the reverse sequence as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99% CI, 0.84–1.32; HR for letrozole followed by tamoxifen, 0.96; 99% CI, 0.76–1.21).[364]

Five trials have studied the use of tamoxifen for 2 to 3 years followed sequentially by a third-generation aromatase inhibitor versus continued tamoxifen in postmenopausal women. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women with breast cancer who had completed 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5

years of endocrine therapy.[365] The HR for relapse strongly favored sequential treatment with anastrozole (HR, 0.35; 95% CI, 0.18–0.68; *P* = .001) with a trend towards fewer deaths (*P* = .10).[365] Updated results from this study show the HR for relapse-free survival as 0.56 (95% CI, 0.35–0.89; *P* = .01); P value for OS analysis remained at 0.1.[366] The IES trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5 years of endocrine therapy.[367] The results at a median of 55.7 months of follow-up demonstrated the superiority of sequential exemestane in DFS (HR, 0.76; 95% CI, 0.66–0.88; *P* = .0001) with a significant difference in OS in only patients with ER-positive tumors (HR, 0.83; 95% CI, 0.69–1.00; log rank *P* = .05). A prospectively planned, combined analysis of 3224 patients enrolled in the ABCSG 8 trial and the Arimidex Nolvadex (ARNO 95) trial has also been reported.[368] Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or 3 years of anastrozole. With 28 months of median follow-up available, event-free survival was superior with crossover to anastrozole (HR, 0.60; 95% CI, 0.44–0.81; *P* = .0009). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 58 months of median follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both DFS (HR, 0.66; 95% CI, 0.44–1.00; *P* = .049) and OS (HR, 0.53; 95% CI, 0.28–0.99; *P* = .045).[351] A meta-analysis of ABCSG 8, ARNO 95, and ITA studies showed significant improvement in OS (HR, 0.71; 95% CI, 0.52-0.98; *P* = .04) with a switch to anastrozole.[369]

The TEAM trial compared treatment of exemestane alone versus sequential therapy of tamoxifen for 2.5 to 3.0 years followed by exemestane to complete 5 years of hormone therapy.[370] At the end of 5 years, 85% of patients in the sequential group versus 86% in the exemestane group were disease free (HR, 0.97; 95% CI, 0.88–1.08; *P* = .60). This is consistent with the data from the BIG 1-98 trial,[364] in which tamoxifen followed by letrozole or the reverse sequence of letrozole followed by tamoxifen was not associated with significant differences in efficacy versus letrozole monotherapy after a median follow-up of 71 months.

Results of the MA-17 trial in 5187 women who had completed 4.5 to 6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor-positive, early-stage breast cancer.[352,371] At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (HR, 0.58; 95% CI, 0.45–0.76; *P* < .001). No difference in OS was demonstrated (HR, 0.82; 95% CI, 0.57–1.19; *P* = .3), although there was a survival advantage in the subset of patients with ALN-positive disease (HR 0.61; 95% CI, 0.38–0.98; *P* = .04). In a separate cohort analysis of the MA-17 trial, the efficacy of letrozole versus placebo was evaluated after un-blinding of the study in the 1579 women who had been randomly assigned to placebo after 4.5 to 6 years of tamoxifen.[372,373] The median time since completion of tamoxifen was 2.8 years. Both DFS and distant DFS were significantly improved in the group receiving letrozole, thereby providing some evidence for the efficacy of letrozole in patients who had received 4.5 to 6 years of tamoxifen therapy followed by no endocrine therapy for an extended period. A formal quality-of-life analysis demonstrated reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.[374,375] No data are available regarding use of aromatase inhibitors for more than 5 years or long-term toxic effects from extended treatment. In addition, the ATLAS

trial data do not provide clear direction for treatment of postmenopausal women.[376] There are no data available to suggest that an aromatase inhibitor for 5 years is better for long-term benefit than 10 years of tamoxifen.

In the extension study of ABCSG trial 6, hormone receptor-positive postmenopausal patients received 5 years of adjuvant tamoxifen and were randomized to 3 years of anastrozole or no further therapy.[377] At a median follow-up of 62.3 months, women who received anastrozole (n = 387) were reported to have a statistically significantly reduced risk of recurrence compared with women who received no further treatment (n = 469; HR, 0.62; 95% CI, 0.40–0.96; *P* = .031).[377]

The differences in design and patient populations among the studies of the aromatase inhibitors do not allow for the direct comparison of the results of these studies. A meta-analysis of adjuvant trials of aromatase inhibitors versus tamoxifen alone versus after 2 or 3 years of tamoxifen documented lower recurrence rates with the aromatase inhibitor-containing regimen, with no clear impact on OS.[378] It is not known whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy.

The optimal duration of aromatase inhibitor treatment is also not known, nor is the optimal use vis-à-vis chemotherapy established. Further, the long-term (greater than 5-year) safety and efficacy of these agents are still under investigation. The various studies are consistent in demonstrating that the use of a third-generation aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumor recurrences, contralateral breast cancer, and distant metastatic disease when used as initial adjuvant therapy, sequential therapy, or extended therapy. The panel finds no compelling evidence that there is meaningful efficacy or toxicity differences between the aromatase inhibitors, anastrozole, letrozole, and exemestane. All three have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant settings.

NCCN Recommendations for Adjuvant Endocrine Therapy for Postmenopausal Women: The NCCN Guidelines for Breast Cancer recommend the following adjuvant endocrine therapy options for women with early-stage breast cancer who are postmenopausal at diagnosis: an aromatase inhibitor as initial adjuvant therapy for 5 years (category 1); and tamoxifen for 2 to 3 years followed by one of the following options: an aromatase inhibitor to complete 5 years of adjuvant endocrine therapy (category 1) or 5 years of aromatase inhibitor therapy (category 2B); or tamoxifen for 4.5 to 6 years followed by 5 years of an aromatase inhibitor (category 1) or consideration of tamoxifen for up to 10 years. In postmenopausal women, the use of tamoxifen alone for 5 years (category 1) or up to 10 years is limited to those who decline or who have a contraindication to aromatase inhibitors.

NCCN Recommendations for Adjuvant Endocrine Therapy for Premenopausal Women: For women premenopausal at diagnosis, the NCCN Guidelines for Breast Cancer recommend 5 years of tamoxifen (category 1) with or without ovarian suppression (category 1) or ovarian suppression plus an aromatase inhibitor for 5 years (category 1). Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries without menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women is to be considered for therapy with an aromatase inhibitor.[379,380]

After 5 years of initial endocrine therapy, for women who are postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the NCCN Panel recommends considering extended therapy with an aromatase inhibitor for up to 5 years (category 1) or based on the data from the ATLAS trial considering tamoxifen for an additional 5 years. For those who remain premenopausal after the initial 5 years of tamoxifen, the panel recommends considering continuing up to 10 years of tamoxifen therapy.

Response to Adjuvant Endocrine Therapy: The measurement of the nuclear antigen, Ki-67 by IHC, gives an estimate of the tumor cells in the proliferative phase (G1, G2, and M phases) of the cell cycle. Studies have demonstrated the prognostic value of Ki-67 as a biomarker and its usefulness in predicting response and clinical outcome.[381] One small study suggests that measurement of Ki-67 after short-term exposure to endocrine treatment may be useful to select patients with tumors resistant to endocrine therapy and those who may benefit from additional interventions.[382] However, these data require larger analytic and clinical validation. In addition, standardization of tissue handling and processing is required to improve the reliability and value of Ki-67 testing. At this time, there is no conclusive evidence that Ki-67 alone, especially baseline Ki-67 as an individual biomarker, helps to select the type of endocrine therapy for an individual patient. Therefore, the NCCN Breast Cancer Panel does not currently recommend assessment of Ki-67.

The cytochrome P-450 (CYP450) enzyme, CYP2D6, is involved in the conversion of tamoxifen to endoxifen. Over 100 allelic variants of *CYP2D6* have been reported in the literature.[383] Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with one or two variant alleles with either reduced or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. A large retrospective study of 1325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen.[384] However, the BIG 1-98 trial reported on the outcome based on CYP2D6 genotype in a subset of postmenopausal patients with endocrine-responsive, early invasive breast cancer.[385] The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.[385] A genetic analysis of the ATAC trial found no association between CYP2D6 genotype and clinical outcomes.[386] Given the limited and conflicting evidence at this time,[387] the NCCN Breast Cancer Panel does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines.[388] When prescribing a selective serotonin reuptake inhibitor (SSRI), it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

Adjuvant Cytotoxic Chemotherapy

Several combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized. All adjuvant chemotherapy regimens listed in the NCCN Guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guidelines does not distinguish between options for chemotherapy regimens by ALN status.

The adjuvant chemotherapy guidelines also include specific representative doses and schedules for the recommended adjuvant chemotherapy regimens. The regimens have been categorized as “preferred” or “other.”

The purpose of distinguishing the adjuvant chemotherapy regimens as preferred and other adjuvant chemotherapy regimens is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens.[389] Factors considered by the panel include the efficacy, toxicity, and treatment schedules of the regimens. Summarized below are clinical trial results focusing on treatment efficacy.

Preferred Regimens

Regimens listed as preferred include: dose-dense doxorubicin and cyclophosphamide (AC) with dose-dense sequential paclitaxel; dose-dense AC followed by sequential weekly paclitaxel; and docetaxel plus cyclophosphamide (TC).

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates, and results from one of the trials showed an improvement in OS, with the addition of paclitaxel.[390,391] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in women with ER-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide vs. doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support or every 3 weeks. The results show no significant difference between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence (P = .01) and a 31% reduction in the hazard of death (P = .013) for the dose-dense regimens.[392]

The ECOG E1199 study was a four-arm trial that randomized 4950 women to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every-3-week schedule or a weekly schedule.[393-395] At a median 63.8 months of follow-up, no statistically significant differences in DFS or OS were observed when comparing paclitaxel to docetaxel or weekly versus every-3-week administration. In a secondary series of comparisons, weekly paclitaxel was superior to every-3-week paclitaxel in DFS (HR, 1.27; 95% CI, 1.03–1.57; P = .006) and OS (HR, 1.32; 95% CI, 1.02–1.72; P = .01), and every-3-week docetaxel was superior to every-3-week paclitaxel in DFS (HR, 1.23; 95% CI, 1.00–1.52; P = .02) but not in OS.[395] Based on these results, as well as the findings from the CALGB trial 9741 that showed dose-dense AC followed by paclitaxel every 2 weeks to have a survival benefit when compared with the regimen of AC followed by every-3-week paclitaxel,[392] the every-3-week paclitaxel regimen has been removed from the guidelines.

Combination TC was compared with AC chemotherapy in a trial that randomized 1016 women with stage I to III breast cancer.[396] At a median follow-up of 7 years, overall DFS (81% vs. 75%; HR, 0.74; 95% CI, 0.56–0.98; P = .033) and OS (87% vs. 82%; HR, 0.69; 95% CI, 0.50–0.97; P = .032) were significantly improved with TC compared with AC.

Other Regimens

Other regimens included in the guidelines are: AC; epirubicin and cyclophosphamide (EC); CMF; AC with sequential docetaxel administered every 3 weeks; AC with sequential weekly paclitaxel; FEC/CEF followed by docetaxel or weekly paclitaxel; FAC followed by weekly paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide (TAC).

The AC regimen for four cycles has been studied in randomized trials, resulting in relapse-free survival and OS equivalent to CMF

chemotherapy.[397,398] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[390,399]

Studies of CMF chemotherapy versus no chemotherapy have shown DFS and OS advantages with CMF chemotherapy.[4,400] Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[401] In the EBCTCG overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (P = .006) and an 11% further reduction in the annual odds of death (P = .02) with anthracycline-containing regimens.[400] Based on these data, the panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients.

The EBCTCG analysis, however, did not consider the potential interaction between HER2 tumor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that are HER2-positive.[277,279,282,328,402-404] The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive has led to a footnote stating that anthracycline-based chemotherapy may be superior to non-anthracycline-containing regimens in the adjuvant treatment of such patients.

A trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[405] This study showed that higher-dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate-dose EC in event-free survival and OS.

The NSABP B-36 phase III trial data compared six cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) with four cycles of AC, both given every 3 weeks as adjuvant therapy in patients with node-negative breast cancer. The rationale for the trial was to determine whether DFS improved with extra cycles of treatments.[406] Patient and tumor characteristics were equally distributed between both arms (<50 years of age: 40%, lumpectomy: 68%, and hormone positivity: 65%).[406] The results reported that DFS after eight years was not greater for those women who had been on the longer FEC chemotherapy treatment and that the women on the FEC experienced greater side effects. Combined grade 3 and 4 toxicities with a significant difference of 3% or more between AC and FEC arms included fatigue 3.55% versus 8.45%, febrile neutropenia 3.70% versus 9.42%, and thrombocytopenia 0.74% versus 4.41%, respectively.[406] Five deaths resulted from the toxicity of FEC treatment, compared to the death of two women on the AC treatment.[406]

The quality-of-life impact and menstrual history of women on the NSABP (NRG) B-36 was also investigated in a phase III trial.[407] Women on FEC treatment experienced a worse quality of life at six months and higher rate of post-chemotherapy amenorrhea.[407]

Based on the results of the NSABP B-36 trial, the NCCN Panel has now *excluded* the FEC/CEF and FAC/CAF regimens as options for adjuvant therapy.

Two randomized prospective trials of FEC chemotherapy in ALN-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive

classic CMF therapy versus FEC chemotherapy using high-dose epirubicin. Both 10-year relapse-free survival (52% vs. 45%; *P* = .007) and OS (62% vs. 58%; *P* = .085) favored the FEC arm of the trial.[408] The second trial compared FEC given intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m^2 vs. 100 mg/m^2) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year DFS (55% vs. 66%; *P* = .03) and OS (65% vs. 76%; *P* =.007) both favored the epirubicin 100 mg/m^2 arm.[409] Another randomized trial in women with ALN-positive breast cancer compared 6 cycles of FEC with 3 cycles of FEC followed by 3 cycles of docetaxel.[346] Five-year DFS (78.4% vs. 73.2%; adjusted *P* = .012) and OS (90.7% vs. 86.7%; *P* = .017) were superior with sequential FEC followed by docetaxel. However, no significant DFS differences were seen in a large randomized study comparing adjuvant chemotherapy with 4 cycles of every-3-week FEC followed by 4 cycles of every-3-week docetaxel with standard anthracycline chemotherapy regimens (eg, FEC or epirubicin followed by CMF) in women with node-positive or high-risk, node-negative, operable breast cancer.[410]

The addition of weekly paclitaxel after FEC was shown to be superior to FEC alone in a randomized study of 1246 women with early-stage breast cancer.[411] The former regimen was associated with a 23% reduction in the risk of relapse compared with FEC (HR, 0.77; 95% CI, 0.62–0.95; *P* = .022), although no significant difference in OS was seen when the two arms were compared at a median follow-up of 66 months.

The phase III E1199 trial compared patients with node-positive or high-risk node-negative breast cancer who received 4 cycles of AC every 3 weeks, followed by either paclitaxel or docetaxel, either weekly or every 3 weeks. The 10-year updated results of this trial showed that incorporation of weekly paclitaxel and docetaxel every 3 weeks was associated with significant improvements in DFS, and marginal improvements in OS, compared with paclitaxel given every 3 weeks. Among patients with triple-negative disease, the10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75%.[412]

Final results from a randomized trial of TAC versus FAC chemotherapy in ALN-positive breast cancer demonstrated that TAC is superior to FAC.[413] Estimated 5-year DFS was 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88; *P* =.001); survival was 87% with TAC and 81% with FAC (HR, 0.70; 95% CI, 0.53–0.91; *P* = .008). DFS favored TAC in both ER-positive and ER-negative tumors. At a median follow-up of 73 months, results from the 3-arm randomized NSABP B-30 trial comparing TAC versus AT versus AC followed by docetaxel (AC followed by T) demonstrated that AC followed by T had a significant advantage in DFS (HR, 0.83; *P* = .006) but not in OS (HR, 0.86; *P* = .086) when compared with TAC. In addition, both DFS (HR, 0.080; *P* = .001) and OS (HR, 0.83; *P* = .034) were significantly increased when AC followed by T was compared with AT, with AT demonstrating non-inferiority compared with TAC.[414]

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[4,320] These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with ER-positive tumors receiving adjuvant endocrine therapy when compared with patients with ER-negative tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with ER-negative disease. For example, the results of Berry et al demonstrated that 22.8% more patients with ER-negative tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with ER-positive tumors receiving chemotherapy.[320]

For women greater than 70 years of age, the consensus of the panel is that there are insufficient data to make definitive chemotherapy recommendations. Although AC or CMF has been shown to be superior to capecitabine in a randomized trial of women aged greater than or equal to 65 years with early-stage breast cancer,[415] the enrollment in that study was discontinued early.[415] Therefore, there is also a possibility that AC/CMF is not superior to any chemotherapy in this cohort. The panel recommends that treatment should be individualized for women in this age group, with consideration given to comorbid conditions.

Adjuvant HER2-Targeted Therapy

The panel recommends HER2-targeted therapy in patients with HER2-positive tumors (see *Principles of HER2 Testing* in the NCCN Guidelines for Breast Cancer). Trastuzumab is a humanized monoclonal antibody with specificity for the extracellular domain of HER2.[416]Results of several randomized trials testing trastuzumab as adjuvant therapy have been reported.[284-289,417-419]

NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every 3 weeks followed by paclitaxel for 4 cycles every 3 weeks or the same regimen with 52 weeks of trastuzumab commencing with paclitaxel. In the NCCTG N9831 trial, patients with HER2-positive breast cancer that was node-positive, or node-negative, with primary tumors greater than 1 cm in size if ER- and PR-negative or greater than 2 cm in size if ER- or PR-positive, were similarly randomized except that paclitaxel was given by a low-dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until the completion of paclitaxel.

The B-31 and NCCTG N9831 trials have been jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with paclitaxel. There were 4045 patients included in the joint analysis performed at 3.9 years median follow-up. A 48% reduction in the risk of recurrence (HR, 0.52; 95% CI, 0.45–0.60; $P < .001$) and a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.50–0.75; log-rank $P = .001$) were documented.[418] Similar significant effects on DFS were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.[287,420,421] In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death in patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial).[284,285,287,289,420,421] The frequency of cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction. An analysis of data from N9831 showed the 3-year cumulative incidence of CHF or cardiac death to be 0.3%, 2.8%, and 3.3% in the arms of the trial without trastuzumab, with trastuzumab following chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.[420] The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials in part reflects rigorous monitoring for cardiac dysfunction. Furthermore, concerns have been raised regarding the long-term cardiac risks associated with trastuzumab therapy based on results of follow-up evaluations of cardiac function in patients enrolled in some of these trials.[422,423]

A third trial (HERA) (N = 5081) tested trastuzumab for 1 or 2 years compared to none following all local therapy and a variety of standard chemotherapy regimens in patients with node-positive disease or node-negative disease with tumor greater than or equal to 1 cm.[285] At a median follow-up of one year, a 46% reduction in the risk of recurrence was reported in those who received trastuzumab compared with those who did not (HR, 0.54; 95% CI, 0.43–0.67; $P < .0001$), there was no

difference in OS, and acceptable cardiac toxicity was reported. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an OS benefit when compared with observation (HR for risk of death = 0.66; 95% CI, 0.47–0.91; *P* = .0115).[424] After this initial analysis, patients randomized to chemotherapy alone were allowed to cross over to receive trastuzumab. Intent-to-treat analysis including a crossover patient was reported at 4-year median follow-up.[419] The primary endpoint of DFS continued to be significantly higher in the trastuzumab-treated group (78.6%) versus the observation group (72.2; HR, 0.76; 95% CI, 0.66–0.87; *P* < .0001). At a median follow-up of 8 years, the study reported no significant difference in DFS, a secondary endpoint, in patients treated with trastuzumab for 2 years compared with 1 year.[286] Therefore, 1 year of adjuvant trastuzumab remains the current standard of treatment.

The BCIRG 006 study randomized 3222 women with HER2-positive, node-positive, or high-risk node-negative breast cancer to AC followed by docetaxel; AC followed by docetaxel plus trastuzumab for one year; or carboplatin, docetaxel, and trastuzumab for one year.[289] At 65-month follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC-TH) had an HR for DFS of 0.64 (*P* < .001) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC-T). The HR for DFS was 0.75 (*P* = .04) when patients in the carboplatin/docetaxel/ trastuzumab (TCH)-containing arm were compared to patients in the control arm. No statistically significant difference in the HR for DFS was observed between the two trastuzumab-containing arms. An OS advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (HR for AC-TH vs. AC-T = 0.63; *P* = .001; HR for TCH vs. AC-T = 0.77; *P* = .04). Cardiac toxicity was significantly lower in the TCH arm (9.4% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18.6%; *P* < .0001). CHF was also more frequent with AC-TH than TCH (2% vs. 0.4%; *P* < .001). Analysis of this trial by critical clinical event revealed more distant breast cancer recurrences with TCH (144 vs. 124) but fewer cardiac events with TCH compared with AC-TH (4 vs. 21).[289] In the FinHer trial, 1010 women were randomized to 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.[284] Patients (n = 232) with HER2-positive cancers that were either node-positive or node-negative and greater than or equal to 2 cm and PR-negative were further randomized to receive or not receive trastuzumab for 9 weeks during the vinorelbine or docetaxel portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (HR, 0.42; 95% CI, 0.21–0.83; *P* = .01). No statistically significant differences in OS (HR, 0.41; 95% CI, 0.16–1.08; *P* = .07) or cardiac toxicity were observed with the addition of trastuzumab.[284] At 5-year follow-up, a comparison of the two arms (ie, chemotherapy with and without trastuzumab) demonstrated that the HRs for distant DFS (HR, 0.65; 95% CI, 0.38–1.12; *P* = .12) and OS (HR, 0.55; 95% CI, 0.27–1.11; *P* = .094) were higher relative to those reported at 3 years.[417]

All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in DFS, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, showed significant improvement in OS with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline. The benefits of trastuzumab are independent of ER status.[287,288] In the FNCLCC-PACS-04 trial, 528 women with HER2-positive, node-positive breast cancer were randomly

assigned to receive trastuzumab or observation *after* completion of adjuvant anthracycline-based chemotherapy with or without docetaxel.[425] No statistically significant DFS or OS benefit was observed with the addition of trastuzumab. These results suggest that the sequential administration of trastuzumab following chemotherapy is not as efficacious as a schedule involving concomitant chemotherapy and trastuzumab. The NCCN Guidelines recommend a total of 12 months of adjuvant trastuzumab as the standard of care. Shorter than 12-month duration has not been found to be as effective[426] and longer than 12 months duration does not have any added benefit; it has been found to be as effective as the 12 months of trastuzumab therapy.[427]

Retrospective analyses of low-risk patients with small tumors demonstrate that in T1a-bN0 breast cancers, HER2 overexpression added a 15% to 30% risk for recurrence.[428-431] These risks rates are substantially higher than seen among similarly sized HER2-negative tumors.

A recent single-arm, multicenter trial studied the benefit of trastuzumab-based chemotherapy in patients with HER2-positive, node-negative tumors less than or equal to 3 cm. All patients received trastuzumab and weekly paclitaxel for 12 weeks, followed by completion of a year of trastuzumab monotherapy.[432] Fifty percent of patients enrolled had tumors less than or equal to 1.0 cm and 9% of patients had tumors that were between 2 and 3 cm. The endpoint of the study was DFS. The results presented at the 2013 Annual San Antonio Breast Cancer Symposium demonstrated that the 3-year DFS rate in the overall population was 98.7% (95% CI, 97.6–99.8; $P < .0001$).

Dual anti-HER2 blockade associated with trastuzumab plus lapatinib and trastuzumab plus pertuzumab has shown significant improvements in the pCR rate when compared with chemotherapy associated with one anti-HER2 agent in the neoadjuvant setting.[268,269,271]

However, in the adjuvant setting, the results of the ALTTO trial failed to demonstrate a significant improvement in DFS with dual anti-HER2 therapy compared with trastuzumab alone.[433] After a median follow-up of 4.5 years, the DFS rates were 86% for patients who received trastuzumab alone; 88% for participants treated with trastuzumab and lapatinib concurrently; and 87% for patients who received trastuzumab followed by lapatinib.[433]

NCCN Recommendation for Adjuvant HER2-Targeted Therapy

Based on these studies, the panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors greater than 1 cm.

The NCCN Panel suggests trastuzumab and chemotherapy be used for women with HER2-positive, node-negative tumors measuring 0.6 to 1.0 cm (ie, T1b) and for smaller tumors that have less than or equal to 2 mm axillary node metastases (pN1mi). Some support for this recommendation comes from studies showing a higher risk of recurrence for patients with HER2-positive, node-negative tumors less than or equal to 1 cm compared to those with HER2-negative tumors of the same size.[428] Ten-year breast cancer-specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, in women with tumors characterized as HER2-positive, ER-positive tumors, and 70% and 61%, respectively, in women with HER2-positive, ER-negative tumors. Two more retrospective studies have also investigated recurrence-free survival in this patient population. None of the patients in these two retrospective studies received trastuzumab. In the first study, 5-year recurrence-free survival rates of 77.1% and 93.7% ($P < .001$) were observed for patients with HER2-positive and

HER2-negative T1a-bN0M0 breast tumors, respectively, with no recurrence-free survival differences seen in the HER2-positive group when hormonal receptor status was considered.[429] In the other retrospective study of women with small HER2-positive tumors, the risk of recurrence at 5 years was low (99% [95% CI; 96%–100%] for HER2-negative disease and 92% [95% CI; 86%–99%] for HER2-positive disease).[434] Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[289,435,436]

NCCN-Recommended HER-Targeted Regimens

The panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred HER2-targeting adjuvant regimen. The TCH regimen is also a preferred regimen, especially for those with risk factors for cardiac toxicity, given the results of the BCIRG 006 study that demonstrated superior DFS in patients receiving TCH or AC followed by docetaxel plus trastuzumab compared with AC followed by docetaxel alone.

Other trastuzumab-containing regimens included in the NCCN Guidelines are: AC followed by docetaxel and trastuzumab,[289] and docetaxel plus trastuzumab followed by FEC[284] (see *Preoperative /Adjuvant Systemic Therapy* in NCCN Guidelines for Breast Cancer for a complete list of regimens).

Considering the unprecedented improvement in OS in the metastatic setting[437] and the significant improvement in pCR seen in the neoadjuvant setting,[269,271] the NCCN Panel considers it reasonable to incorporate pertuzumab into the above adjuvant regimens, if the patient did *not* receive pertuzumab as a part of neoadjuvant therapy. An ongoing study is evaluating pertuzumab and trastuzumab with standard chemotherapy regimens in the adjuvant setting.[438,439]

The NCCN Panel has included paclitaxel and trastuzumab as an option for patients with low-risk, HER2-positive, stage 1 tumors. This is based on a trial that studied this combination in 406 patients with small, node-negative, HER2-positive tumors. The results showed that the 3-year rate of DFS was 98.7% (95% CI, 97.6–99.8) and the risk of serious toxic effects with this regimen was low (incidence of heart failure reported was 0.5%).[440]

Adjuvant Therapy for Tumors of Favorable Histologies

The guidelines provide systemic treatment recommendations for the favorable histology of invasive breast cancers, such as tubular and mucinous cancers, based on tumor size and ALN status. If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology of breast cancers. The vast majority of tubular breast cancers are both ER-positive and HER2-negative. Thus, the pathology evaluation and accuracy of the ER and/or HER2 determination should be reviewed if a tubular breast cancer is ER-negative and/or HER2-positive, or if a tumor with an ER- and PR-negative status is grade 1.[17] Should a breast cancer be histologically identified as a tubular or mucinous breast cancer and be confirmed as ER-negative, then the tumor should be treated according to the guideline for the usual histology, ER-negative breast cancers. The panel acknowledges that prospective data regarding systemic adjuvant therapy of tubular and mucinous histologies are lacking.

Systemic Therapy for Triple-Negative Breast Cancer

For women with triple-negative breast cancer, several clinical trials sought to determine whether the addition of carboplatin (alone or in combination) as neoadjuvant chemotherapy can improve outcomes for women with triple-negative breast cancer. In the German GeparSixto

trial, 315 patients with triple-negative breast cancer were administered neoadjuvant therapy consisting of weekly paclitaxel plus non-pegylated liposomal doxorubicin with bevacizumab and then randomly assigned to additional treatment with weekly carboplatin.[441] The addition of carboplatin achieved a pCR rate of 59% compared with pCR of 38% in patients who did not receive carboplatin.[441]

In the CALGB 40603 randomized phase II trial, 443 patients with stage II to III triple-negative breast cancer received standard anthracycline- and taxane-based chemotherapy with or without carboplatin and with or without bevacizumab. Compared with standard chemotherapy, the addition of carboplatin resulted in significantly higher pCR rate (54% vs. 41%, OR 1.71).[442] The addition of bevacizumab increased the numeric rate of pCR but was not statistically significant (with bevacizumab, pCR was 52% [95% CI; 45%–58%] and without bevacizumab pCR was 44% [95% CI; 38%–51%]; *P* = .057). In this study,[442] as well as in the GeparSixto study,[441] the addition of carboplatin and/or bevacizumab led to increased rates of adverse events. Neutropenia and thrombocytopenia were more common with carboplatin. Hypertension and postsurgical complications were more common with bevacizumab.

Even though the results of randomized trials show improvement in pCR rates when carboplatin is added to anthracycline- and taxane-based chemotherapy, the long-term outcomes such as OS or DFS associated with the incorporation of carboplatin are not yet known. Therefore, at this time, the NCCN Panel does not recommend addition of carboplatin to neoadjuvant standard chemotherapy for patients with triple-negative breast cancer outside a clinical trial setting.

Medullary Carcinoma

Medullary carcinoma is an uncommon variant of infiltrating ductal carcinoma characterized by high nuclear grade, lymphocytic infiltration, a pushing tumor border, and the presence of a syncytial growth pattern. It was previously thought that medullary carcinoma has a lower potential for metastases and a better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk of metastases equals that of other high-grade carcinomas, even for cases that meet all the pathologic criteria for typical medullary carcinoma. Furthermore, typical medullary carcinoma is uncommon, and there is marked interobserver variation in diagnosing this entity. Many cases classified as medullary carcinoma do not have all the pathologic features on subsequent pathologic review. Given these facts, there is concern that patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as typical medullary carcinoma and this classification is used as the basis for withholding otherwise indicated adjuvant systemic therapy. Therefore, the NCCN Panel believes that including medullary carcinoma with other special histology cancers that carry a favorable prognosis and often do not require systemic therapy is not appropriate. The panel recommends that cases classified as medullary carcinoma be treated as other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

Post-Therapy Surveillance and Follow-up

See page MS-48.

Stage III Invasive Breast Cancer

Staging and Workup

The staging evaluation for most patients with stage III invasive breast cancer is similar to the one for patients with T3, N1, M0 disease. The workup includes history and physical exam, a CBC, liver function and alkaline phosphatase tests, chest imaging, pathology review, and pre-chemotherapy determination of tumor ER/PR receptor status and HER2 status. Diagnostic bilateral mammogram and breast ultrasound

should be performed as clinically warranted. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

The performance of other studies, such as a breast MRI, a bone scan (category 2B), and abdominal imaging with diagnostic CT (with or without pelvic CT) or MRI (all category 2A) are optional unless directed by symptoms or other abnormal study results. PET/CT scan is also included as an optional additional study (category 2B). Ultrasound is an alternative when diagnostic CT or MRI is unavailable.

The consensus of the panel is that FDG PET/CT is most helpful in situations where standard imaging results are equivocal or suspicious. However, limited studies[132,133,443-447] support a potential role for FDG PET/CT to detect regional node involvement as well as distant metastases in locally advanced breast cancer, including T3, N1, M0 disease.

A retrospective study comparing bone scan with integrated FDG PET/CT, in women with stages I–III breast cancer with suspected metastasis, observed a high concordance (81%) between the two studies for reporting osseous metastases.[448] The NCCN Panel suggests that bone scan may be omitted if FDG PET/CT results are positive for bone metastases.

Equivocal or suspicious sites identified by PET/CT scanning should be biopsied for confirmation whenever possible and if the site of disease would impact the course of treatment. In the past decade, the advent of PET/CT scanners has significantly changed the approach to PET imaging.[449] However, the terminology has also created confusion regarding the nature of the scans obtained from a PET/CT device. PET/CT scanners have both a PET and CT scanner in the same gantry that allows precise coregistration of molecular (PET) and anatomic (CT) imaging. Almost all current clinical PET imaging is performed using combined PET/CT devices.

In PET/CT tomographs, the CT scanner has a second important role beyond diagnostic CT scanning.[449] For PET applications, the CT scan is also used for photon attenuation correction and for anatomic localization of the PET imaging findings. For these tasks, the CT scan is usually taken without breathholding, to match PET image acquisition, and typically uses low-dose (non-diagnostic) CT. Radiation exposure for these non-diagnostic CT scans is lower than for diagnostic CT. Intravenous contrast is not needed for this task.

PET/CT scanners typically include a high-quality CT device that can also be used for stand-alone, optimized, and fully diagnostic CT. Diagnostic CT scans are acquired using breathholding for optimal chest imaging, and are often performed with intravenous contrast. For fully diagnostic CT, the CT beam current, and therefore patient radiation exposure, is considerably higher than for the low-dose CT needed for PET requirements. Radiation exposures for fully diagnostic CT are often greater than for the emission (PET) component of the study.

Currently, the approach to clinical PET/CT imaging varies widely across centers.[450] Many centers perform low-dose CT as part of a PET/CT scan, and perform optimized, fully diagnostic CT only when diagnostic CT has also been requested in addition to PET/CT. Other centers combine diagnostic CT scans with PET on all of their PET/CT images. The CT scans described in the workup section of the guidelines refer to fully optimized diagnostic CT scans, while the PET or PET/CT scans refer to scans primarily directed towards the PET component, not necessarily using diagnostic-quality CT. It is important for referring

physicians to understand the differences between PET/CT performed primarily for PET imaging and fully optimized CT performed as a stand-alone diagnostic CT examination.[450] It may be convenient to perform PET/CT and diagnostic CT at the same time.

Operable Locally Advanced Breast Cancer

(Clinical stage T3, N1, M0)

Locally advanced breast cancer describes a subset of invasive breast cancer where the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. The AJCC clinical staging system used in these guidelines and for the determination of operability is recommended, and locally advanced disease is represented by the stage III category. Patients with stage III disease may be further divided into: 1) those where an initial surgical approach is unlikely to successfully remove all disease or to provide long-term local control; and 2) those with disease where a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, stage IIIA patients are divided into those who have clinical T3, N1, M0 disease versus those who have clinical T any, N2, M0 disease, based on evaluation by a multidisciplinary team.

Postsurgical systemic adjuvant therapy for patients with stage IIIA breast cancer who do not receive neoadjuvant chemotherapy is similar to that for patients with stage II disease.

Inoperable Locally Advanced Breast Cancer

(Clinical stage IIIA [except for T3, N1, M0], clinical stage IIIB, or clinical stage IIIC)

For patients with inoperable, non-inflammatory, locally advanced disease at presentation, the initial use of anthracycline-based preoperative systemic therapy with or without a taxane is standard therapy.[451] Patients with locally advanced breast cancer that is HER2-positive should receive an initial chemotherapy program that incorporates preoperative trastuzumab and possibly pertuzumab. Local therapy following a clinical response to preoperative systemic therapy usually consists of: 1) total mastectomy with level I/II ALN dissection, with or without delayed breast reconstruction; or 2) lumpectomy and level I/II axillary dissection.

Both local treatment groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. Without detected internal mammary node involvement, consideration may be given to include the internal mammary lymph nodes in the radiation field (category 2B). Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completed preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease. Up to one year of total trastuzumab therapy should be completed if the tumor is HER2-positive (category 1). Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

Patients with an inoperable stage III tumor with disease progression during preoperative systemic therapy should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy after local therapy is felt to be standard. Tamoxifen (or an aromatase inhibitor if postmenopausal) should be added for those with hormone receptor-positive tumors, and trastuzumab should be given to those with HER2-positive tumors. Post-treatment follow-up for women with stage III disease is the same as for women with early-stage invasive breast cancer.

Post-Therapy Surveillance and Follow-up for Stage I-III

Post-therapy follow-up is optimally performed by members of the treatment team and includes the performance of regular history/physical examinations every 4 to 6 months for the first 5 years after primary therapy and annually thereafter. Mammography should be performed annually.

Regarding frequency of mammograms after breast-conserving surgery followed by radiation, the NCCN Panel agrees with ASTRO's "Choosing Wisely' list of recommendations released in 2014.[452] The recommendations state that "annual mammograms are the appropriate frequency for surveillance of breast cancer patients who have had breast-conserving surgery and radiation therapy with no clear advantage to shorter interval imaging. Patients should wait 6 to 12 months after the completion of radiation therapy to begin their annual mammogram surveillance. Suspicious findings on physical examination or surveillance imaging might warrant a shorter interval between mammograms."

The NCCN panel notes that any imaging of reconstructed breast is not indicated.

According to the NCCN Panel, in the absence of clinical signs and symptoms suggestive of recurrent disease, laboratory or imaging studies to screen for metastasis are not necessary. The routine performance of alkaline phosphatase tests and LFTs are not included in the guidelines.[453-455] In addition, the panel notes no evidence to support the use of "tumor markers" for breast cancer, and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.[132,456]

The use of breast MRI in follow-up of women with prior breast cancer is undefined. It may be considered as an option in women with high lifetime risk (greater than 20% based on models largely dependent on family history) of developing a second primary breast cancer. Rates of contralateral breast cancer after either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA1/2* mutations when compared with patients with sporadic breast cancer.[457-459]

The panel recommends that women with intact uteri who are taking adjuvant tamoxifen should have yearly gynecologic assessments and rapid evaluation of any vaginal spotting that might occur because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women.[460] The performance of routine endometrial biopsy or ultrasonography in the asymptomatic woman is not recommended. Neither test has demonstrated utility as a screening test in any population of women. The vast majority of women with tamoxifen-associated uterine carcinoma have early vaginal spotting.

If an adjuvant aromatase inhibitor is considered in women with amenorrhea following treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be performed if endocrine therapy with an aromatase inhibitor is initiated.[379] Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered prior to initiating therapy with an aromatase inhibitor in a young woman.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI) has been studied and is an effective intervention in decreasing hot flashes.[461-464] There is evidence suggesting that concomitant use of

tamoxifen with certain SSRIs (eg, paroxetine, fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[465,466] These SSRIs/SNRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of CYP2D6. However, the mild CYP2D6 inhibitors such as citalopram, escitalopram, sertraline, and venlafaxine appear to have no or only minimal effect on tamoxifen metabolism.[379,467,468]

Follow-up also includes assessment of patient adherence to ongoing medication regimens such as endocrine therapies. Predictors of poor adherence to medication include the presence of side effects associated with the medication, and incomplete understanding by the patient of the benefits associated with regular administration of the medication.[469] The panel recommends the implementation of simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits, as well as brief, clear explanations on the value of taking the medication regularly and the therapeutic importance of longer durations of endocrine therapy.

Lymphedema is a common complication after treatment for breast cancer. Factors associated with increased risk of lymphedema include extent of axillary surgery, axillary radiation, infection, and patient obesity.[470,471] The panel recommends educating the patients on lymphedema, monitoring for lymphedema, and referring for lymphedema management as needed.

Many young women treated for breast cancer maintain or regain premenopausal status following treatment for breast cancer. For these women, the NCCN Panel discourages the use of hormonal birth control methods, regardless of the hormone receptor status of the tumor.[472] Alternative birth control methods are recommended, including intrauterine devices, barrier methods, and, for those with no intent of future pregnancy, tubal ligation or vasectomy for the partner. Breastfeeding during endocrine or chemotherapy treatment is not recommended by the NCCN Panel because of risks to the infant. Breastfeeding after breast-conserving treatment for breast cancer is not contraindicated. However, lactation from an irradiated breast may not be possible, or may occur only with a diminished capacity.[472,473]

The panel recommends that women on an adjuvant aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter. The use of estrogen, progesterone, or selective ER modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. A single phase 3 study, ABCSG12, demonstrated improved outcomes with the addition of zoledronic acid in premenopausal women receiving endocrine therapy with ovarian suppression.[474] Use of bisphosphonates in such patients and in other subgroups remains controversial. Denosumab has shown to significantly reduce fractures in postmenopausal women receiving adjuvant therapy aromatase inhibitors, and improves bone mineral density.[475]

Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

Evidence suggests that a healthy lifestyle may lead to better breast cancer outcomes. A nested case control study of 369 women with

ER-positive tumors who developed a second primary breast cancer compared with 734 matched control patients who did not develop a second primary tumor showed an association between obesity (body mass index [BMI] ≥30), smoking, and alcohol consumption and contralateral breast cancer.[476] A prospective study of 1490 women diagnosed with stage I–III breast cancer showed an association between high fruit and vegetable consumption, physical activity, and improved survivorship, regardless of obesity.[477] There is emerging evidence that obesity is associated with poorer outcomes for certain subtypes of breast cancers. The study by the Women's Intervention Nutrition group randomized early-stage breast cancer patients to an intervention group and a control group. The intervention consisted of eight one-on-one visits with a registered dietitian who had been trained on a low-fat eating plan. OS analysis showed no significant difference between the two study arms (17% for the intervention vs. 13.6% without); however, subgroup analysis showed that those with ER- and PR-negative disease who were part of the intervention group saw a 54% improvement in OS.[478]

The NCCN Panel recommends an active lifestyle and ideal body weight (BMI 20–25) for optimal overall health and breast cancer outcomes as there are reports of proven benefits of exercise and active lifestyle during and after treatment.[479-481]

For management of issues related to survivorship including late/long-term effects of cancer and its treatment, see the NCCN Guidelines for Survivorship.

Stage IV Metastatic or Recurrent Breast Cancer

Staging and Workup

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam; the performance of a CBC, LFTs, chest diagnostic CT, bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan; consideration of diagnostic CT of the abdomen (with or without diagnostic CT of the pelvis) or MRI scan of the abdomen; and biopsy documentation of first recurrence if possible. The panel generally discourages the use of sodium fluoride PET or PET/CT scans for the evaluation of patients with recurrent disease, except in those situations where other staging studies are equivocal or suspicious. There is limited evidence (mostly from retrospective studies) to support the use of PET/CT scanning to guide treatment planning through determination of the extent of disease in select patients with recurrent or metastatic disease.[132,133,482,483] The panel considers biopsy of equivocal or suspicious sites to be more likely than PET/CT scanning to provide accurate staging information in this population of patients.

The consensus of the panel is that FDG PET/CT is optional (category 2B) and most helpful in situations where standard imaging results are equivocal or suspicious. The NCCN Panel recommends bone scan or sodium fluoride PET/CT to detect bone metastases (category 2B). However, if the FDG PET results clearly indicate bone metastasis, these scans can be omitted.

The NCCN Panel recommends that metastatic disease at presentation or first recurrence of disease should be biopsied as a part of the workup for patients with recurrent or stage IV disease. This ensures accurate determination of metastatic/recurrent disease and tumor histology, and

allows for biomarker determination and selection of appropriate treatment.

Determination of hormone receptor status (ER and PR) and HER2 status should be repeated in all cases when diagnostic tissue is obtained. ER and PR assays may be falsely negative or falsely positive, and there may be discordance between the primary and metastatic tumors.[484,485] The reasons for the discordance may relate to change in biology of disease, differential effect of prior treatment on clonal subsets, tumor heterogeneity, or imperfect accuracy and reproducibility of assays.[485] Discordance between the receptor status of primary and recurrent disease has been reported in a number of studies. The discordance rates are in the range of 3.4% to 60% for ER-negative to ER-positive; 7.2% to 31% for ER-positive to ER-negative; and 0.7% to 11% for HER2.[486-495]

The NCCN Panel recommends that re-testing the receptor status of recurrent disease be performed, *especially* in cases when it was previously unknown, originally negative, or not overexpressed. For patients with clinical courses consistent with hormone receptor–positive breast cancer, or with prior positive hormone receptor results, the panel has noted that a course of endocrine therapy is reasonable, regardless of whether the receptor assay is repeated or the result of the most recent hormone receptor assay.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer, as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

Management of Local Disease Only

Patients with local recurrence only are divided into 3 groups: those who had been treated initially by mastectomy alone, those who had been treated initially by mastectomy plus radiation therapy, and those who had received breast-conserving therapy.

In one retrospective study of local recurrence patterns in women with breast cancer who had undergone mastectomy and adjuvant chemotherapy without radiation therapy, the most common sites of local recurrence were at the chest wall and the supraclavicular lymph nodes.[496] The recommendations for treatment of the population of patients experiencing a local recurrence only are supported by analyses of a combined database of patients from the EORTC 10801 and Danish Breast Cancer Cooperative Group 82TM trials. The analyses compared breast-conserving therapy with mastectomy in patients with stage I and stage II disease. The 133 (approximately 8%) patients experiencing a local recurrence as an initial event were approximately equally divided between those who had undergone mastectomy and those who had received breast-conserving therapy as initial treatment for breast cancer. Of those in the former group, 51 (76%) were able to undergo radiation therapy with or without surgery as treatment for local disease recurrence. No difference in survival emerged between patients receiving treatment after initial treatment with mastectomy or breast-conserving therapy; approximately 50% of both groups were alive at 10-year follow-up.[497]

According to the NCCN Panel, mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished without heroic surgery) and involved-field radiation therapy to the chest wall and supraclavicular area (if the chest wall was not previously treated or if additional radiation therapy may be safely

administered). The use of surgical resection in this setting implies the use of limited excision of disease with the goal of obtaining clear margins of resection. Unresectable chest wall recurrent disease should be treated with radiation therapy if no prior radiation has been given. Women with a local recurrence of disease after initial breast-conserving therapy should undergo a total mastectomy and axillary staging if a level I/II axillary dissection was not previously performed. Limited data suggest that a repeat SLN biopsy following local recurrence of disease may be successfully performed in 80% of women who have previously undergone breast-conserving therapy and sentinel node biopsy.[498] The consensus of the panel is that the preferred surgical approach for most women with a local recurrence following breast-conserving therapy and sentinel node biopsy is mastectomy and a level I/II axillary dissection, although sentinel node biopsy in lieu of a level I/II axillary dissection can be considered if prior axillary staging was done by sentinel node biopsy only.

The results of the CALOR trial found that after complete resection in patients with isolated locoregional recurrence, adjuvant chemotherapy improves both DFS and OS.[499] After median follow-up of 4.9 years, the overall DFS was 69% in the chemotherapy group versus 57% in the group that did not receive chemotherapy (HR = 0.59, *P* = .046).[499] Five-year OS in all patients in the study was also significantly improved with chemotherapy (88% vs. 76%, *P* = .024).[499] The benefit of adjuvant chemotherapy was mostly seen in women with ER-*negative* disease. Among women with ER-negative disease, 5-year DFS was 67% versus 35% (HR, 0.32; 95% CI, 0.14–0.73) and in those ER-positive disease, the 5-year DFS was 70% versus 69% (HR, 0.94; 95% CI, 0.47–1.89).[499]

According to the NCCN Panel, after local treatment, women with local recurrences only should be considered for limited duration systemic chemotherapy or endocrine therapy similar to that outlined in the adjuvant chemotherapy section. The panel emphasized the importance of individualizing treatment strategies in patients with a recurrence of disease limited to a local site.

Management of Stage IV or Recurrent Metastatic Disease

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.[500]

Guideline Stratification for Therapy in Systemic Disease

Patients with recurrence of breast cancer or metastatic breast cancer at diagnosis are initially stratified according to whether bone metastasis is present. These two patient subsets are then stratified further by tumor hormone receptor and HER2 status.

Supportive Therapy for Bone Metastases

Treatment targeting osteoclast activity is of value in patients with metastatic breast cancer in bone to prevent bone fractures, bone pain requiring radiation therapy, spinal cord compression, and hypercalcemia (skeletal-related events; SREs).[501-503] The bisphosphonates zoledronic acid or pamidronate have been used for this purpose, and there is extensive clinical trial support for their efficacy in prevention of SREs (see section below on *Bisphosphonates*). Denosumab is a fully human monoclonal antibody directed against RANK ligand, a mediator of osteoclast function.[504] A single, randomized, active, controlled trial in metastatic breast cancer showed equivalency and superiority of time to the occurrence of SRE with denosumab, as compared with zoledronic acid.[503] No study of bisphosphonate or denosumab has demonstrated an impact on OS in patients with metastatic disease.

The bisphosphonates and denosumab are associated with a risk of development of osteonecrosis of the jaw (ONJ). Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ. Thus, a dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonate or denosumab, and dental procedures during treatment should be avoided if at all possible. Additional risk factors for the development of ONJ include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[505]

Confirmation of metastatic disease by imaging, including x-ray, diagnostic CT, or MRI, and initial evaluation of serum calcium, creatinine, phosphorous, and magnesium levels should be undertaken prior to the initiation of intravenous bisphosphonate treatment or subcutaneous denosumab treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous, and magnesium may be prudent since hypophosphatemia and hypocalcemia have been reported.

Bisphosphonates

An intravenous bisphosphonate (eg, pamidronate, zoledronic acid) in combination with oral calcium citrate and vitamin D supplementation should be used in women with bone metastasis, especially if lytic and/or in weight-bearing bone, if expected survival is 3 months or longer, and if creatinine levels are below 3.0 mg/dL (category 1).[502,506-511] Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.[512,513]

There are extensive data from randomized trials in support of the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data include the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.[509,511,513-518] In metastatic bone disease, bisphosphonate treatment is associated with fewer SREs, fewer pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.

The use of bisphosphonates in metastatic disease is a palliative care measure. No impact on OS has been observed in patients treated with bisphosphonates. The data indicate that zoledronic acid and pamidronate may be given on a 3- to 5-week schedule in conjunction with antineoplastic therapy (ie, endocrine therapy, chemotherapy, biologic therapy). Recent data from a phase III study showed zoledronic acid administered once every 12 weeks versus the current standard of once every four weeks does not compromise efficacy among women with breast cancer and bone metastases. The SRE rate was 22% when zoledronic acid was administered every 4 weeks versus 23.2% when administered once every 12 weeks.[519]

The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500 mg and vitamin D_3 of 400 to 800 IU. Recommended agents for use in the United States are pamidronate 90 mg intravenously over 2 hours or zoledronic acid 4 mg intravenously over 15 minutes. The original studies continued treatment for up to 24 months; however, there are limited long-term safety data indicating treatment can continue beyond that time.[516,518,520] The risk of renal toxicity necessitates monitoring of serum creatinine prior to administration of each dose and dose reduction or discontinuation if renal function is reduced. Current clinical trial results support the use of bisphosphonates for up to 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials.

ONJ, a complication of bisphosphonate treatment, has been described. In a review of more than 16,000 cancer patients, an increased risk for jaw or facial bone surgery along with an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw with the use of intravenous bisphosphonates was documented. An absolute risk of 5.48 events per 100 patients treated was seen, with an increase in risk associated with an increase in cumulative dose of drug.[521] It is recommended that patients should undergo a dental examination with preventive dentistry prior to initiation of bisphosphonate therapy.

Denosumab

Women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy may also be considered for treatment with denosumab (category 1). This recommendation is based on the results of a single randomized trial comparing denosumab to zoledronic acid.[503] All trial patients were recommended to supplement with vitamin D and calcium. Patients on the experimental arm were given 120 mg of denosumab injected subcutaneously every 4 weeks plus intravenous placebo versus the control arm where patients were given an intravenous infusion of 4 mg of zoledronic acid every 4 weeks, and a subcutaneous placebo. In this trial with non-inferiority as the primary endpoint, denosumab was shown to significantly delay time to first SRE by 18% as compared with zoledronic acid (HR, 0.82; 95% CI, 0.71–0.95; $P < .001$ for non-inferiority; $P = .01$ for superiority) and time to first and subsequent SREs (rate ratio, 0.77; 95% CI, 0.66–0.89; $P = .001$). No difference in time to progression or OS was observed. Adverse event profiles were similar for the two groups, including incidence of ONJ, with a reduced risk of renal-related and acute phase adverse events in the denosumab treatment group. Long-term risks of denosumab treatment are unknown. The optimal duration of treatment with denosumab is not known.

Endocrine Therapy for Stage IV or Recurrent Metastatic Disease

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy.

In premenopausal women without previous exposure to an antiestrogen, initial treatment is with selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women.[522] In premenopausal women who received a prior endocrine therapy within 12 months, the preferred second-line therapy is ovarian ablation or suppression followed by endocrine therapy as for postmenopausal women.

Endocrine therapies for recurrent/stage IV disease in postmenopausal women include nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); serum ER modulators (tamoxifen or toremifene); ER down-regulators (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol) and recently several new combination therapies with novel agents have become available such as exemestane with everolimus, palbociclib in combination with fulvestrant, and palbociclib with letrozole.

According to some studies, in postmenopausal women, aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.[523-526] A Cochrane review has also suggested a survival benefit favoring the aromatase inhibitors over other endocrine therapies, although the advantage is small.[527] A randomized phase III trial comparing tamoxifen with exemestane as first-line endocrine therapy for postmenopausal women with metastatic breast cancer showed no significant differences in progression-free survival (PFS) or OS between the two arms.[525]

Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen.[528,529] A randomized phase II study compared anastrozole versus fulvestrant in over 200 patients with advanced breast cancer.[530,531] In the initial analysis, fulvestrant was as effective as anastrozole in terms of overall response (36.0% vs. 35.5%; odds ratio, 1.02; 95% CI, 0.56 –1.87; *P* = .947) in evaluable patients (n = 89 for fulvestrant and n = 93 for anastrozole).[530] An improved time to progression was seen with fulvestrant compared to anastrazole (median time to progression was 23.4 months for fulvestrant vs. 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; *P* = .0496).[531] This study used a higher 500 mg loading dose every 2 weeks for 3 doses and then 500 mg monthly.[530] The median OS was observed to be longer in the fulvestrant group than in the anastrozole group (54.1 months vs. 48.4 months; HR, 0.70; *P* = .041).[532] These findings are currently being studied in a prospective phase III trial (ClinicalTrials.gov identifier: NCT01602380).

A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression following aromatase inhibitor therapy documented a partial response rate of 14.3% with an additional 20.8% of patients achieving stable disease for at least 6 months.[533] The clinical benefit rates of exemestane and fulvestrant observed in a phase III trial of postmenopausal women with hormone receptor-positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy were comparable (32.2% vs. 31.5%; *P* = .853).[534] In that study, fulvestrant was administered as a 500 mg loading dose followed by doses of 250 mg on day 14, day 28, and then monthly.

A separate phase III randomized study in postmenopausal women with metastatic ER-positive breast cancer compared fulvestrant 500 mg every 2 weeks for 3 doses followed by 500 mg monthly versus fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR, 0.80; 95% CI, 0.68–0.94; *P* = .006),[535] indicating an increased duration of response with the higher dose of fulvestrant. The final analyses demonstrated an increase in median OS (4.1 months) and reduced risk of death (19%) with a dose of 500 mg compared with 250 mg. Median OS was 26.4 versus 22.3 months (HR, 0.81; 95% CI, 0.69–0.96; *P* = .02).[536]

Combination endocrine therapy in postmenopausal women with hormone receptor-positive, previously *untreated* metastatic breast cancer has been reported from two studies comparing single-agent anastrozole versus anastrozole plus fulvestrant.

In one study (FACT), combination endocrine therapy was not superior to single-agent anastrozole (time to progression HR, 0.99; 95% CI, 0.81–1.20; *P* = .91).[537] In the second study (S0226), PFS (HR, 0.80; 95% CI, 0.68–0.94; stratified log-rank *P* = .007) and OS (HR, 0.81; 95% CI, 0.65–1.00; stratified *P* = .049) were superior with combination anastrozole plus fulvestrant.[538] An unplanned subset analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest benefit. The reason for the divergent outcomes in these two studies is not known.

A phase III trial studied the effect of fulvestrant alone or in combination with anastrozole or exemestane in patients with advanced breast cancer and an acquired non-steroidal aromatase inhibitor-resistant disease.[539] An aromatase inhibitor had been given as adjuvant treatment to 18% of patients for a median of 27.9 months, and to 82% of patients for locally advanced/metastatic disease for a median of 19.3 months. Median PFS was 4.8 months, 4.4 months, and 3.4 months for patients treated with fulvestrant alone, anastrazole plus fulvestrant, and fulvestrant plus exemestane, respectively. No differences were

observed for overall response rate, clinical benefit rate, and OS. This trial provides no evidence that adding an aromatase inhibitor to fulvestrant in patients with non-steroidal aromatase inhibitor-resistant disease improves the results achieved with fulvestrant alone. In postmenopausal women who have received previous antiestrogen therapy and are within one year of antiestrogen exposure, there is evidence supporting the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.[540,541]

Palbociclib, a highly selective inhibitor of CDK 4/6 kinase activity, has a role in treating women with ER-positive metastatic breast cancer in combination with endocrine therapy. A phase II, open-label, randomized, multicenter trial evaluated the safety and efficacy of palbociclib in combination with letrozole versus letrozole alone as first-line treatment for patients with advanced ER-positive, HER2- negative breast cancer.[542] Median PFS reported was double with the combination regimen compared to letrozole alone (20.2 months for the palbociclib plus letrozole group and 10.2 months for the letrozole alone group; HR, 0.488; 95% CI, 0.319–0.748).[542] Grade 3/4 adverse reactions reported at a higher incidence in the palbociclib plus letrozole versus letrozole alone group included neutropenia (54% vs. 1%) and leukopenia (19% vs. 0%). Based on this study, the FDA approved palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

The phase III trial (PALOMA-3) compared the combination of palbociclib and fulvestrant to fulvestrant in pre- or post-menopausal hormone receptor-positive, HER2-negative advanced breast cancer patients, whose disease progressed on prior endocrine therapy. Pre- or peri-menopausal patients also received goserelin. The median PFS was 9.2 months for the combination compared to 3.8 months for fulvestrant (HR 0.42, P < .000001) with similar discontinuation rates because of adverse effects (2.6% and 1.7%, respectively).[543] Grade 3/4 adverse events of palbociclib and fulvestrant were mainly confined to neutropenia with the same low incidence (0.6%) of febrile neutropenia in both arms. OS data from this trial are immature.[543]

The NCCN Panel has included the combination of palbociclib with letrozole as a first-line endocrine therapy option for postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer. In addition, the recently updated version includes palbociclib with fulvestrant as a category 1 option for women with hormone receptor-positive (post-menopausal or premenopausal women receiving ovarian suppression with an LHRH agonist), HER2-negative metastatic breast cancer who have progressed on endocrine therapy.

Limited studies document a PFS advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with hormone receptor-positive metastatic breast cancer that is HER2-positive.[544,545]

Resistance to endocrine therapy in women with hormone receptor-positive disease is frequent. One mechanism of resistance to endocrine therapy is activation of the mammalian target of rapamycin (mTOR) signal transduction pathway. Several randomized studies have investigated the use of aromatase inhibition in combination with inhibitors of the mTOR pathway.

A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with hormone receptor-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.[546] After a

median follow-up of 13 months, an intent-to-treat analysis showed that the clinical benefit was 42.1% (95% CI, 29.1–55.9) with tamoxifen alone and 61.1% (95% CI, 46.9–74.1) with tamoxifen plus everolimus. An improvement in median time to progression was seen when everolimus was combined with tamoxifen compared with tamoxifen alone. Median time to progression was 4.5 months (95% CI, 3.7–8.7) with tamoxifen alone versus 8.5 months (95% CI, 6.01–13.9) with everolimus and tamoxifen.[546]

A phase III trial in postmenopausal women with advanced, hormone receptor-positive breast cancer with no prior endocrine therapy for advanced disease, randomized subjects to letrozole with or without the mTOR inhibitor temsirolimus has been reported.[547] In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; long-rank *P* = .18).

The results of this trial differ from that of the BOLERO-2 trial (described below). The reasons for the differences in the outcomes of these two randomized phase III studies[547,548] is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with hormone receptor-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase inhibitor to exemestane with or without the mTOR inhibitor everolimus.[549] Final results reported after median 18-month follow-up show that median PFS (by central review) remained significantly longer with everolimus plus exemestane versus placebo plus exemestane at 11.0 versus 4.1 months, respectively; (HR, 0.38; 95% CI, 0.31–0.48; *P* < .0001).[548] The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.[548,549] Analysis of safety and efficacy in the elderly patients enrolled in this trial showed that elderly patients treated with an everolimus-containing regimen had similar incidences of these adverse events, but the younger patients had more on-treatment deaths.[550] Based on the evidence from the BOLERO-2 trial, the NCCN Panel has included everolimus plus exemestane as an option for women who fulfill the entry criteria for BOLERO-2.

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women with breast cancers who respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at disease progression. After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy. Additional endocrine therapies for second-line and subsequent therapy are listed in the NCCN Guidelines for Breast Cancer.

Endocrine therapy may be active in patients with negative ER and PR determinations, especially on the primary tumor and in soft tissue disease and/or bone-dominant disease.[551-553] Endocrine therapy is associated with relatively low toxicity. Further false-negative determinations of ER and PR tumor status are not unusual and the hormone receptor status of primary and metastatic sites of disease may differ. Therefore, the NCCN Breast Cancer Panel recommends consideration of a trial of endocrine therapy for patients with disease characterized as hormone receptor-negative with disease localized to the bone or soft tissue only or with asymptomatic visceral disease, irrespective of HER2 tumor status.

Cytotoxic Chemotherapy for Stage IV or Recurrent Metastatic Disease

Women with hormone receptor-negative tumors not localized to the bone or soft tissue only, that are associated with symptomatic visceral metastasis, or that have hormone receptor-positive tumors that are refractory to endocrine therapy should receive chemotherapy. A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm. Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single-agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity and is of little survival benefit.[554-558] Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression. Limited information suggests that PFS can be prolonged with the use of continuous chemotherapy versus shorter-course chemotherapy.[559,560] Due to the lack of consistent OS differences, the use of prolonged versus shorter chemotherapy needs to be weighed against the detrimental effects of continuous chemotherapy on overall quality of life.

Single cytotoxic agents and combination chemotherapy regimens recommended by the panel for the treatment of patients with metastatic disease are listed in the NCCN Guidelines.

Single Agents

Single agents are categorized as either preferred or other single agents based on a balance of the efficacy, toxicity, and treatment schedules of the drugs. Among preferred single agents, the panel includes: the anthracyclines, doxorubicin, epirubicin, and pegylated liposomal doxorubicin; the taxanes, paclitaxel, docetaxel, and albumin-bound paclitaxel; anti-metabolites, capecitabine and gemcitabine; and non-taxane microtubule inhibitors, eribulin and vinorelbine.

Eribulin is a non-taxane microtubule inhibitor used for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. In a phase III trial, 762 patients with metastatic breast cancer were randomized 2:1 to eribulin or treatment of physicians' choice. One-year OS was 53.9% for patients receiving eribulin versus 43.7% for the control arm, and median OS was 13.12 versus 10.65 months, representing a 19% statistically significant risk reduction (P = .041). Time to progression was greater with eribulin 3.7 versus 2.2 months for patients in the control arm (P = .14).[561]

Several studies have demonstrated that eribulin is active in metastatic breast cancer. A large randomized trial of heavily pre-treated patients with metastatic breast cancer compared treatment with eribulin versus therapy of physician's choice. Eribulin demonstrated significant improvement in OS with 2.5-month prolongation of median OS (median OS for patients treated with eribulin was 13.1 months compared with 10.6 months for those receiving other treatments. HR, 0.81; 95% CI, 0.66–0.99; P = .041).[561]

A phase III trial compared eribulin with capecitabine in patients with metastatic breast cancer. While a survival advantage was observed with eribulin treatment in all sub-groups of patients, there was a significant survival advantage observed with eribulin over capecitabine among patients with HER2-negative (15.9 vs. 13.5 months; HR 0.84; 95% CI

0.72, 0.98; *P* = .03) and triple-negative (14.4 vs. 9.4 months; HR 0.70; 95% CI 0.55, 0.91; *P* = .01) breast cancer.[562]

Among other single agents, the panel includes: cyclophosphamide, carboplatin, docetaxel, albumin-bound paclitaxel, cisplatin, ixabepilone, and epirubicin.

Ixabepilone, an epothilone B analogue, is also used for treatment of recurrent or metastatic breast cancer as a single agent. Use of ixabepilone as monotherapy has been evaluated in several phase II trials of women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy [563]; in patients with taxane-resistant metastatic breast cancer[564]; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[565] In the phase II trials, objective response rate, median duration of response, and median OS duration were 41.5% (95% CI, 29.4%–54.4%), 8.2 months (95% CI, 5.7–10.2 months), and 22.0 months (95% CI, 15.6–27.0 months) in the first-line setting;[563] 12% (95% CI, 4.7%– 26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients;[564] and 11.5% (95% CI, 6.3%–18.9%), 5.7 months, and 8.6 months for the patients previously treated with an anthracycline, a taxane, and capecitabine.[565] In the study by Perez et al,[565] grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).

Combination Regimens

Among combination regimens, the panel includes FAC/CAF; FEC; AC; EC; CMF; docetaxel, capecitabine; gemcitabine, paclitaxel; gemcitabine, carboplatin; and paclitaxel, bevacizumab.

A series of trials have sought to define the role for bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor in the treatment of metastatic breast cancer. The E2100 trial randomized 722 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.[566] This trial documented superior PFS (11.8 months vs. 5.9 months; HR 0.60; *P* <.001) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. A similar trial enrolled 736 patients who were randomized to treatment with docetaxel and bevacizumab or docetaxel and placebo.[567] This trial also documented increased PFS in the arm containing bevacizumab (10.1 months vs. 8.2 months with docetaxel alone; HR 0.77; *P* = .006). An additional trial, RIBBON-1, combined bevacizumab with capecitabine, with a taxane (docetaxel, nab-paclitaxel), with anthracyclines (FEC, CAF, AC, or EC), or with the same chemotherapy alone. Results of this trial show a statistically significant increase in PFS with bevacizumab and capecitabine (8.6 months vs. 5.7 months; HR, 0.69; *P* < .001) and taxane- or anthracycline- (9.2 months vs. 8.0 months; HR, 0.64; *P* < .001) containing arms.[568,569] None of these studies demonstrates an increase in OS or quality of life when analyzed alone or in a meta-analysis combining the trials.[570] The increase in PFS with bevacizumab is modest, and appears the greatest in combination with paclitaxel, especially as reported in an unpublished analysis provided to the FDA.[571]

As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guidelines include doses and schedules of these single agents and combination regimens for metastatic breast cancer. Failure to achieve a tumor response to 3 sequential chemotherapy regimens or ECOG performance status of 3 or greater is an indication for supportive therapy only. In this context, failure to respond to a chemotherapy regimen means the absence of

even a marginal response to the use of a given chemotherapy regimen. Response to a chemotherapy regimen followed by progression of disease is not considered a failure to experience response.

Patients with metastatic breast cancer frequently develop many anatomically localized problems that may benefit from local irradiation, surgery, or regional chemotherapy (eg, intrathecal methotrexate for leptomeningeal carcinomatosis).

HER2-Targeted Therapy for Stage IV or Recurrent Metastatic Disease

Patients with tumors that are HER2-positive may derive benefit from treatment with HER2-targeted therapy. The panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by ISH or 3+ by IHC. HER2 testing recommendations are described in the guideline. Patients with tumors IHC 0 or 1+ for HER2 or ISH not amplified have very low rates of HER2-targeted response and HER2-targeted therapy.[572] Adequate standardization and validation of HER2 assays by ISH and IHC used in clinical practice is a concern, and data suggest that false-positive determinations are common.[22,23,573-575] Recommendations regarding HER2 testing have been published.[573,575]

First-Line Regimens for HER2-Positive Tumors

The NCCN Panel has categorized HER2-targeting regimens as either preferred or other.

Preferred First-Line Regimens

A randomized, double-blind, phase III study compared the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel versus trastuzumab and docetaxel as first-line treatment for HER2-positive metastatic breast cancer.[576] The primary endpoint of the study was independent assessment of PFS. The secondary endpoints were PFS assessed by investigator, objective response rate, OS, and safety. A total of 808 patients were enrolled in this trial.[576] The addition of pertuzumab provided a statistically significant improvement in PFS compared to trastuzumab plus docetaxel alone. The median independently assessed PFS was increased by 6.1 months, from 12.4 months in the control group to 18.5 months in the pertuzumab group (HR for progression or death, 0.62; 95% CI, 0.51– 0.75; $P < .001$).[576] At a median follow-up of 30 months the results showed a statistically significant improvement in OS in favor of the pertuzumab-containing regimen, with a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.52–0.84; $P = .0008$). The median OS was 37.6 months in the non-pertuzumab group and had not yet been reached in the pertuzumab-containing regimen.[437] The most common adverse reactions reported in the pertuzumab group compared to the control group were diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. Peripheral edema and constipation were greater in the control group.[576] Cardiac adverse events or left ventricular systolic dysfunction were reported slightly more frequently in the control group.[577] Health-related quality of life was not different in the two treatment groups.[578]

Phase II trials have also found activity and tolerability for pertuzumab, pertuzumab with trastuzumab, and for other regimens combining pertuzumab and trastuzumab together with other active cytotoxics (ie, paclitaxel, vinorelbine).[579,580,581] Phase III trials of pertuzumab plus chemotherapy without trastuzumab have not been reported.

The NCCN Panel recommends pertuzumab plus trastuzumab in combination with a taxane as a preferred option for first-line treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab plus trastuzumab in combination with docetaxel is an NCCN category 1 and in combination with paclitaxel is an NCCN category 2A recommendation.

Other First-Line Regimens for HER2-Positive Tumors

First-line trastuzumab in combination with selected chemotherapeutics[291] or as a single agent[290,292] is another option for HER2-positive metastatic breast cancer patients. Randomized trials demonstrate benefit from adding trastuzumab to other agents including paclitaxel with or without carboplatin,[291,572,582,583] docetaxel,[582] and vinorelbine,[582] or as a single agent[292] for patients with HER2-positive disease. In addition, the combination of trastuzumab and capecitabine has also shown efficacy as a first-line trastuzumab-containing regimen in this population of patients.[584,585] For those patients with hormone receptor-positive, HER2-positive disease, the panel recommends initial treatment with endocrine therapy, an approach consistent with most of these studies. The panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial.[291,585,586]

T-DM1 is an antibody-drug conjugate. Through a stable linker, the HER2-targeting antitumor property of trastuzumab is conjugated with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine).

A randomized, international, multicenter, open-label, phase III study (EMILIA) evaluated the safety and efficacy of T-DM1 compared with lapatinib plus capecitabine for HER2-positive patients with locally advanced breast cancer or metastatic breast cancer previously treated with trastuzumab and a taxane.[587] The primary endpoints of this study were PFS, OS, and safety. T-DM1 demonstrated a statistically significant improvement in both primary endpoints of PFS and OS. PFS (assessed by independent review) was significantly improved with T-DM1 with median PFS of 9.6 months vs. 6.4 months with lapatinib plus capecitabine; HR for progression or death from any cause was 0.65 (95% CI, 0.55–0.77; $P < .001$). At the first interim analysis, T-DM1 also demonstrated significant improvement in OS. The stratified HR for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI, 0.48–0.81; $P = .0005$).[587] Rates of grade 3 or 4 adverse events were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1 (frequency >25%), whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.[587]

In a phase III trial (MARIANNE), 1,095 patients with locally advanced or metastatic breast cancer were randomized to first-line treatment with T-DM1 with or without pertuzumab or to treatment with trastuzumab plus a taxane. The primary endpoints were safety and PFS assessed by independent review. The PFS for T-DM1 with pertuzumab was found non-inferior to trastuzumab and a taxane (15.2 and 13.7 months respectively; HR, 0.87; 97.5% CI, 0.69–1.08; $P = .14$).[588] The PFS for T-DM1 alone was non-inferior to trastuzumab plus a taxane (14.1 and 13.7, respectively; HR, 0.91; 97.5% CI, 0.73–1.13; $P = .31$).[588] The incidence of Grade 3–5 adverse events was 54.1%, 45.4%, and 46.2% in the trastuzumab plus a taxane arm, T-DM1 arm, and T-DM1 plus pertuzumab arm, respectively. Health-related quality of life was maintained for a longer duration with a median of 7.7 months for T-DM1 (HR, 0.70; 95% CI, 0.57–0.86) and a median of 9 months for T-DM1 plus pertuzumab (HR, 0.68; 95% CI, 0.55–0.84) compared with a median of 3.9 months for trastuzumab and a taxane.[588]

Based on the MARIANNE trial data demonstrating T-DM1 and T-DM1 with pertuzumab being non-inferior, with better QOL compared with trastuzumab plus taxane and possibly better-tolerated for some

patients, [588] the NCCN Panel included T-DM1 as one of the first-line options for treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab, trastuzumab, and a taxane, however, remains the preferred frontline regimen for HER2-positive metastatic disease based on data demonstrating improved OS compared to trastuzumab and a taxane. TDM-1 as first-line therapy should be considered only in those not suitable for the preferred treatment.

Regimens for Trastuzumab-Exposed HER2-Positive Disease

The NCCN Panel recommends continuation of HER2 blockade for patients with HER2-positive metastatic breast cancer that progresses on first-line trastuzumab-containing regimens. This recommendation also applies to patients who are diagnosed with HER2-positive metastatic disease after prior exposure to trastuzumab in the adjuvant setting. Several trials have demonstrated benefit of continuation of trastuzumab therapy following disease progression on a trastuzumab-containing regimen.[589-591] However, the optimal duration of trastuzumab in patients with long-term control of disease is unknown.

The NCCN Guidelines include doses and schedules of representative regimens for use in HER2-positive metastatic breast cancer.

Pertuzumab is active in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study (n = 66) show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy.[592] The trial reported an objective response rate of 24.2% (16 patients out of 66). The overall median PFS time observed with pertuzumab and trastuzumab combination was 15.5 months (range, 0.9–17.0 months; 80% CI, 18–31 months.[592] The reported median duration of response with the combination was 5.8 months (range, 2.9–15.3 months).[592]

To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of patients (n = 29) whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, patients with disease progression (n = 17) continued to receive pertuzumab with the addition of trastuzumab. In the 29 patients who received pertuzumab monotherapy, the objective response rate and clinical benefit rate reported were 3.4% and 10.3%, respectively, whereas in the patients who received dual blockade after progression on pertuzumab, the objective response rate and clinical benefit rate were 17.6% and 41.2%, respectively.[593]

According to the NCCN Panel, for patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (such as vinorelbine or taxane) may be considered. Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

The regimen of capecitabine plus lapatinib is also an option for patients with HER2-positive disease following progression on a trastuzumab-containing regimen. A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or metastatic breast cancer refractory to trastuzumab in the metastatic setting and with prior treatment with an anthracycline and a taxane in either the metastatic or adjuvant setting.[594] Time to progression was increased in the group receiving combination therapy when compared with the group receiving capecitabine monotherapy (8.4 months vs. 4.4 months; HR, 0.49; 95% CI, 0.34–0.71; $P < .001$). The patients who progressed on monotherapy were allowed to cross over to the combination arm. This resulted in insufficient power to detect significant

differences in OS; an exploratory analysis demonstrated a trend toward a survival advantage with lapatinib plus capecitabine.[595] The analysis reported a median OS of 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (HR, 0.87; 95% CI, 0.71–1.08; *P* = .210).[595]

Another study of women with metastatic breast cancer showed that lapatinib in combination with letrozole increased PFS over letrozole alone in the subset of women with HER2-positive cancer (3.0 months for letrozole and placebo vs. 8.2 months for letrozole and lapatinib; HR, 0.71; 95% CI, 0.53–0.96; *P* = .019).[544] In addition, results from a phase III trial in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy were randomly assigned to monotherapy with lapatinib or trastuzumab plus lapatinib showed that PFS was increased from 8.1 weeks to 12 weeks (*P* = .008) with the combination.[596] The OS analysis data showed that lapatinib plus trastuzumab improved median survival by 4.5 months, with median OS of 14 months for the combination therapy and 9.5 months for lapatinib alone (HR, 0.74; 95% CI, 0.57–0.97; *P* = .026). [597] This improvement in OS analysis included patients who were initially assigned to monotherapy and crossed over to receive combination therapy at the time of progression.[597]

Based on the absence of data, the panel does not recommend the addition of chemotherapy to the trastuzumab and lapatinib combination.

Surgery for Stage IV or Recurrent Metastatic Disease

The primary treatment approach recommended by the NCCN Panel for women with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment for those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.[598] Generally such surgery should be undertaken only if complete local clearance of tumor may be obtained and if other sites of disease are not immediately threatening to life. Alternatively, radiation therapy may be considered as an option to surgery. Often such surgery requires collaboration between the breast surgeon and the reconstructive surgeon to provide optimal cancer control and wound closure.

Retrospective studies suggest a potential survival benefit from complete excision of the in-breast tumor in select patients with metastatic breast cancer.[599-602] Substantial selection biases exist in all of these studies and are likely to confound the study results.[603,604] Two recent prospective, randomized studies assessed whether or not surgery on the primary tumor in the breast is necessary for women who are diagnosed with metastatic/stage IV breast cancer. The results from both studies presented at the 2013 Annual San Antonio Breast Cancer Symposium were similar showing that surgical treatment of primary tumors in women presenting with stage IV disease does not produce an increase in OS.[605,606]

Nevertheless, the panel recognizes the need for randomized clinical trials that will address the risks and benefits of local therapy for patients with stage IV disease while eliminating selection biases. Patient enrollment in such trials is encouraged.

Distant Sites of Recurrence Requiring Consideration of Therapies Local to the Metastatic Site

Surgery, radiation, or regional chemotherapy (eg, intrathecal methotrexate) may be indicated as needed for localized clinical scenarios such as brain metastases, leptomeningeal disease, choroid metastases, pleural effusion, pericardial effusion, biliary obstruction,

ureteral obstruction, impending pathologic fracture, cord compression, localized painful bone, or soft-tissue disease.

The guidelines include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3). There have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.[607,608] While there is heterogeneity among the study results, a series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone.[607] No differences in OS have been demonstrated. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (eg, the monitoring of temperatures and management of possible tissue burns). The panel thus recommends that the use of hyperthermia be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the panel and is a category 3 recommendation.

Monitoring Metastatic Disease

Monitoring the treatment of metastatic breast cancer involves a wide array of assessments and the need for the clinician to integrate several different forms of information to make a determination of the effectiveness of treatment and the acceptability of toxicity. The information includes those from direct observations of the patient, including patient-reported symptoms, performance status, change in weight, and physical examination; laboratory tests such as alkaline phosphatase, liver function, blood counts, and calcium; radiographic imaging; functional imaging; and, where appropriate, tumor biomarkers. The results of these evaluations generally are classified as response, continued response to treatment, stable disease, uncertainty regarding disease status, or progression of disease. The clinician typically must assess and balance multiple different forms of information to make a determination regarding whether disease is being controlled and the toxicity of treatment is acceptable. Sometimes this information may be contradictory.

The panel recommends using widely accepted criteria for reporting response, stability, and progression of disease such as the RECIST criteria[609] and the WHO criteria.[610] The NCCN Panel also recommends using the same method of assessment over time. For example, an abnormality initially found on diagnostic CT scan of the chest should be monitored with repeat diagnostic CT scans of the chest.

The optimal frequency of testing is uncertain, and is primarily based on the monitoring strategies utilized in breast cancer clinical trials. The page titled *Principles of Monitoring Metastatic Disease* in the algorithm provides a table outlining general recommendations for the frequency and type of monitoring as a baseline before initiation of new therapy, for monitoring the effectiveness of cytotoxic chemotherapy and endocrine therapy, and as an assessment when there is evidence of disease progression. The panel has indicated in a footnote that the frequency of monitoring can be reduced in patients who have long-term stable disease. These are guidelines and should be modified for the individual patient using clinical judgment, especially for those with stable or responding disease for long periods of time.

The clinical use of Circulating Tumor Cells (CTC) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor

PFS and OS.[611] In spite of its prognostic ability, CTC count has failed to show a predictive value. A prospective, randomized, phase 3 trial (SWOG S0500) evaluated the clinical utility of serial enumeration of CTC in patients with metastatic breast cancer. [611] According to the study results, switching to an alternative cytotoxic therapy after 3 weeks of first-line chemotherapy in patients with persistently increased CTC did not affect either PFS or OS.[611]

Special Situations

Paget's Disease

Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the NAC.[612] It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. There is an associated cancer elsewhere in the breast in up to about 80% to 90% of cases.[613-615] The associated cancers are not necessarily located adjacent to the NAC and may be either DCIS or invasive cancer.

Women with clinical signs that raise suspicion for Paget's disease require a complete history and physical examination and diagnostic breast imaging. Any breast lesion identified by imaging or examination should be evaluated according to the NCCN Guidelines for Breast Screening and Diagnosis. The skin of the NAC should undergo surgical biopsy, including the full thickness of the epidermis including at least a portion of any clinically involved NAC. When biopsy of the NAC is positive for Paget's disease, breast MRI is recommended to define the extent of disease and identify additional disease.[615,616]

There are no category 1 data that specifically address local management of Paget's disease. Systemic therapy is based on the stage and biological characteristics of any underlying cancer, and is supported by the evidence cited in the relevant stage-specific breast cancer treatment guidelines.

Management of Paget's disease has traditionally been total mastectomy with axillary dissection. Total mastectomy remains a reasonable option for patients regardless of the absence or presence of an associated breast cancer.[614] Data demonstrate that satisfactory local control may be achieved with breast-conserving surgery including the excision with negative margins of any underlying breast cancer along with resection of the NAC followed by whole breast radiation therapy.[617-621] The risk of ipsilateral breast recurrence after breast-conserving NAC resection and radiation therapy with or without an associated cancer is similar to that with breast-conserving surgery and radiation therapy with the typical invasive or in situ cancer.

For Paget's disease without an associated cancer (ie, no palpable mass or imaging abnormality), it is recommended that breast-conserving surgery consist of removal of the entire NAC with a negative margin of underlying breast tissue. In cases with an associated cancer elsewhere in the breast, the surgery includes removal of the NAC with a negative margin and removal of the peripheral cancer using standard breast-conserving technique to achieve a negative margin. It is not necessary to remove the NAC and the peripheral cancer in continuity in a single surgical specimen or through a single incision. Mastectomy also remains an appropriate treatment option.

ALN staging is not necessary when breast-conserving therapy is used to treat Paget's disease with underlying DCIS without evidence of invasive cancer following clinical examination, imaging evaluation, and

full-thickness skin biopsy of the involved NAC. In the presence of an underlying invasive breast cancer treated with breast-conserving surgery, axillary surgery should be performed according to the *Surgical Axillary Staging* outlined in the NCCN Guidelines. In cases treated by total mastectomy, axillary staging is recommended for patients with invasive disease and should also be considered for patients with underlying DCIS without evidence of invasive disease. This is because the final pathology may reveal an invasive cancer in the mastectomy specimen and the mastectomy precludes subsequent sentinel node biopsy. Two retrospective studies have provided evidence for a high degree of accuracy in the identification of the sentinel node(s) in patients with Paget's disease.[622,623] Patients treated with breast conservation should receive whole breast radiation. Extended-field radiation to regional lymph nodes should be used in cases of an associated invasive breast cancer with involved lymph nodes as for any breast cancer as described in the initial sections of the NCCN Guidelines. A radiation boost should be considered for the site of the resected NAC and any associated resected cancer site, if applicable.

Women with an associated invasive cancer have substantial risk of developing metastases. Adjuvant systemic therapy should be administered according to the stage of the cancer. Women with Paget's disease treated with breast conservation and without an associated cancer or those with associated ER-positive DCIS should consider tamoxifen for risk reduction. Those with an associated invasive cancer should receive adjuvant systemic therapy based on the stage and hormone receptor status.

Phyllodes Tumors of the Breast
(also known as phyllodes tumors, cystosarcoma phyllodes)

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements.[624] Phyllodes tumors exist in benign, borderline, and malignant subtypes, although there is not uniform agreement on the criteria for assigning subtype or for predicting biological behavior.[625] The subtype of phyllodes tumor appears less important for risk of recurrence than does the margin of tumor-free resection achieved by surgical treatment. Diagnosis of phyllodes tumors prior to excisional biopsy/lumpectomy is uncommon. Phyllodes tumors occur in an older age distribution than fibroadenoma, a younger age distribution than the invasive ductal and lobular cancers, and with a mean age of 40.[626] Phyllodes tumors often enlarge rapidly and are usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and FNA cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma.[626] Thus, in the setting of a large or rapidly enlarging clinical fibroadenoma, excisional biopsy should be considered to pathologically exclude a phyllodes tumor. Patients with Li-Fraumeni syndrome (germline *TP53* mutation, see NCCN Guidelines for Genetic/Familial High Risk Assessment) have an increased risk for phyllodes tumors.[627] Local recurrences of phyllodes tumors are the most common site of recurrence. Most distant recurrences occur in the lung, and may be solid nodules or thin-walled cavities.

Treatment of phyllodes tumors (which includes benign, borderline, and malignant subtypes) is with local surgical excision with tumor-free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy. Total mastectomy is necessary only if negative margins cannot be obtained by lumpectomy or partial mastectomy.[628] Since phyllodes tumors rarely metastasize to the ALNs, surgical axillary staging or ALN dissection is not necessary unless the lymph nodes are pathologic on clinical examination.[629] In those patients who experience a local recurrence, resection of the recurrence with wide, tumor-free surgical margins should be performed. Some panel members recommend local radiation therapy of the remaining breast or

chest wall following resection of a local recurrence, but this recommendation is controversial (category 2B).[630]
While the epithelial component of most phyllodes tumors contains ER (58%) and/or PR (75%),[631] endocrine therapy has no proven role in the treatment of phyllodes tumors. Similarly, there is no evidence that adjuvant cytotoxic chemotherapy provides benefit in reduction of recurrences or death. In the rare patient who experiences a systemic recurrence (usually in the lung), treatment should be as recommended in the NCCN Guidelines for Soft Tissue Sarcoma.

Breast Cancer During Pregnancy

Breast cancer occurring concurrently with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births.[632] Unfortunately, breast cancer during pregnancy is most often ALN-positive and with larger primary tumor size. Histologically the tumors are poorly differentiated, are more frequently ER/PR-negative, and approximately 30% are HER2-positive.[633,634] The diagnosis is often delayed because neither the patient nor the physician suspects malignancy.

Evaluation of the pregnant patient with suspected breast cancer should include a physical examination with particular attention to the breast and regional lymph nodes. Mammogram of the breast with shielding can be done safely and the accuracy is reported to be greater than 80%.[635] Ultrasound of the breast and regional lymph nodes can be used to assess the extent of disease and also to guide biopsy. Ultrasound has been reported to be abnormal in up to 100% of breast cancers occurring during pregnancy.[635] Biopsies for cytologic evaluation of a suspicious breast mass may be done with FNA of the breast and suspicious lymph nodes. However, the preferred technique is core needle biopsy. This provides tissue for histologic confirmation of invasive disease as well as adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. The staging studies should be tailored to minimize fetal exposure to radiation. For clinically node-negative T1-T2 tumors, a chest x-ray (with shielding), liver function and renal function assessment, and a CBC with differential are appropriate. In patients who have clinically node-positive or T3 breast lesions, in addition to the aforementioned, an ultrasound of the liver and consideration of a screening MRI of the thoracic and lumbar spine without contrast may be employed. The documentation of the presence of metastases may alter the treatment plan and influence the patient's decision regarding maintenance of the pregnancy. Assessment of the pregnancy should include a maternal fetal medicine consultation and review of antecedent maternal risks such as hypertension, diabetes, and complications with prior pregnancies. Documentation of fetal growth and development and fetal age by means of ultrasonographic assessment is appropriate. Estimation of the date of the delivery will help with systemic chemotherapy planning. In addition, maternal fetal medicine consultation should include counseling regarding maintaining or terminating pregnancy. Counseling of the pregnant patient with breast cancer should include a review of the treatment options, which include mastectomy or breast-conserving surgery as well as the use of systemic therapy. The most common surgical procedure has been modified radical mastectomy. However, breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period,[636] and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.[636,637] When surgery is performed at 25 weeks of gestation or later, obstetrical and prenatal specialists must

be onsite and immediately available in the event of precipitous delivery of a viable fetus.

Although there are a limited number of isolated case reports and small retrospective studies evaluating use of SLN biopsy in pregnant patients,[638,639] the sensitivity and specificity of the procedure has not been established in this setting. Thus, there are insufficient data on which to base recommendations for its use in pregnant women. Decisions related to use of SLN biopsy in pregnancy should be individualized. A review of the relative and absolute contraindications to sentinel node biopsy concluded that sentinel node biopsy should not be offered to pregnant women under 30 weeks gestation.[640] There are limited data with only case reports and estimations of fetal radiation dose regarding use of radioactive tracer (eg, technetium 99m sulfur colloid).[641-643] Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is discouraged during pregnancy.

The indications for systemic chemotherapy are the same in the pregnant patient as in the non-pregnant breast cancer patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The largest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.[644,645] Collected data of chemotherapy exposure in utero indicate that the first trimester has the greatest risk of fetal malformation.[646,647] Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring prior to each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery in order to avoid the potential for hematologic complications during delivery. Data from a single-institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m^2 IV days 1 and 4, doxorubicin 50 mg/m^2 by IV infusion over 72 hours, and cyclophosphamide 500 mg/m^2 IV day 1) may be given with relative safety during the second and third trimesters of pregnancy.[645] As reported by Gwyn et al, the median gestational age at delivery was 38 weeks, more than 50% of the patients had a vaginal delivery, and there were no fetal deaths.[633] An update of this experience reported on 57 women treated with FAC in the adjuvant or neoadjuvant setting. There were 57 live births. A survey of parents/guardians reported on the health of 40 children. There was one child with Down syndrome and two with congenital abnormalities (club foot, congenital bilateral ureteral reflux). The children are reported to be healthy and progressing well in school.[645,648] Ondansetron, lorazepam, and dexamethasone can be used as part of the pre-chemotherapy antiemetic regimen.

There are limited data on the use of taxanes during pregnancy.[649-652] If used, the NCCN Panel recommends weekly administration of paclitaxel after the first trimester if clinically indicated by disease status. There are only case reports of trastuzumab use during pregnancy.[653-660] The majority of these case reports indicated oligo- or anhydramnios with administration of trastuzumab; fetal renal failure occurred in one case. If trastuzumab is otherwise indicated, it should be administered in the postpartum period; the panel recommends against its use during pregnancy.

A single case report of first trimester exposure to lapatinib during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate.[661]

Endocrine therapy and radiation therapy are contraindicated during pregnancy. Endocrine therapy and radiation therapy, if indicated, should thus not be initiated until the postpartum period.

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and for every treatment decision point for the patient.

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States.[662,663] IBC is a clinical diagnosis that requires erythema and dermal edema (peau d'orange) of a third or more of the skin of the breast.

IBC is usually hormone receptor-negative and is more frequently HER2-positive than the usual ductal breast cancers. Studies on gene expression profiling of IBC have demonstrated that all the subtypes of IBC exist, but basal and HER2 overexpressed are more frequent.[664-667] According to the 7th edition of the AJCC Cancer Staging Manual, IBC is classified as stage IIIB, stage IIIC, or stage IV breast cancer, depending on the degree of nodal involvement and whether distant metastases are present. The primary tumor of IBC is classified as T4d by definition, even when no mass is specifically apparent in the breast. On radiographic imaging, findings of skin thickening and, in some cases, an underlying mass are observed. Despite use of the term "inflammatory," the characteristic clinical features of IBC are due to blockage of dermal lymphatics by tumor emboli. Although a biopsy is required to evaluate for the presence of cancer in breast tissue and the dermal lymphatics, a diagnosis of IBC is based on clinical findings, and dermal lymphatic involvement is neither required, nor sufficient by itself, to assign a diagnosis of IBC.[11,668] The differential diagnosis includes cellulitis of the breast and mastitis.

In the past, IBC has often been placed under the general heading of locally advanced breast cancer. There is a growing body of evidence that IBC patients, when compared with noninflammatory forms of locally advanced breast cancer, are more likely to have a less favorable prognosis[669-671] and to be younger at the time of disease presentation.[672]

The NCCN Panel acknowledges that studies focusing on genetic characterization of IBC are needed to more clearly define IBC as a disease entity and to optimize treatment.[673,674] Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC.

StageT4d, N0- N3, M0

Workup

Women with a clinical/pathologic diagnosis of IBC without distant metastasis (stage T4d, N0-N3, M0) should undergo a thorough staging evaluation by a multidisciplinary team.

Recommendations for workup include a complete history and physical examination involving a CBC and platelet count.

A pathology review and pre-chemotherapy determinations of tumor hormone receptor and HER2 receptor status should be performed. HER2 has a predictive role in determining which patients with IBC will benefit from HER2-targeted therapy. The NCCN Panel endorses the CAP protocol for pathology reporting (www.cap.org) and endorses the ASCO CAP recommendations for quality control performance of HER2 testing and interpretation of IHC and ISH results.[575]

Imaging studies help facilitate image-guided biopsy, delineate locoregional disease, and identify distant metastases. Evaluation of all women suspected with IBC must include diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional.

Evaluations for the presence of distant metastasis in the asymptomatic patient include LFTs, bone scan or sodium fluoride PET/CT (category 2B), and diagnostic CT imaging of the chest, abdomen, and pelvis (category 2B; category 2A for diagnostic CT imaging of the chest when pulmonary symptoms are present).

FDG PET/CT may be most helpful in situations where standard imaging results are equivocal or suspicious. However, there is limited evidence suggesting that PET/CT may be a useful adjunct to standard imaging of IBC due to the increased risk of regional lymph node involvement and distant spread of disease in this group of patients.[132,133,675,676] Nevertheless, equivocal or suspicious sites identified by FDG PET/CT scanning or other imaging methods should be biopsied for confirmation of stage IV disease whenever possible. FDG PET/CT is a category 2B recommendation. The consensus of the panel is that FDG PET/CT can be performed at the same time as diagnostic CT. If FDG PET and diagnostic CT are performed and both clearly indicate bone metastases, bone scan or sodium fluoride PET/CT may not be needed.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

Treatment

The treatment of patients with IBC should involve a combined modality approach[662] comprising preoperative systemic therapy followed by surgery (mastectomy) and radiotherapy.

Preoperative Chemotherapy

There are no large randomized trials evaluating the optimal systemic treatment of IBC, since it is a rare disease. The systemic therapy recommendations are based on data from retrospective analyses, small prospective studies, and data from non-IBC, locally advanced breast cancer.

The benefit of preoperative systemic therapy followed by mastectomy over preoperative systemic therapy alone in patients with IBC was shown in a retrospective analysis in which lower local recurrence rates and longer disease-specific survival were reported for the combined modality approach.[677] Results from a large retrospective study of patients with IBC performed over a 20-year period at The University of Texas M.D. Anderson Cancer Center demonstrated that initial treatment with doxorubicin-based chemotherapy followed by local therapy (ie, radiation therapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year DFS rate of 28%.[678]

A retrospective study demonstrated that the addition of a taxane to an anthracycline-based regimen improved PFS and OS in patients with ER-negative IBC.[679] A systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pCR.[680] A study of IBC patients, with cytologically confirmed ALN metastases, treated with anthracycline-based chemotherapy with or without a taxane indicated that more patients receiving the anthracycline-taxane combination achieved a pCR compared with those who received only anthracycline-based therapy. In addition, patients who had a pCR in the ALNs had superior OS and DFS compared with those with residual axillary disease.[681]

The NCCN Panel recommends preoperative systemic therapy with an anthracycline-based regimen with or without taxanes for the *initial* treatment of patients with IBC. The panel also recommends completing the planned chemotherapy prior to mastectomy. If the chemotherapy

was not completed preoperatively, it should be completed postoperatively.

Targeted Therapy

All women with hormone receptor-positive IBC are recommended to receive endocrine therapy sequentially after completing the planned preoperative systemic therapy.

HER2-positive IBC is associated with a poor prognosis.[666,682] For women with HER2-positive disease, the addition of trastuzumab to primary systemic chemotherapy is associated with better response rates.[683-687] A prospective study that randomized women with locally advanced breast cancers, including those with IBC, to neoadjuvant anthracycline-based chemotherapy with or without trastuzumab for 1 year demonstrated that the addition of trastuzumab significantly improved the response rate and event-free survival.[683] The NCCN Panel recommends inclusion of trastuzumab in the chemotherapy regimen and is recommended for patients with HER2-positive disease. There are no available data to indicate the optimal duration of trastuzumab, specifically among women with IBC. However, based on the available data,[683] the panel recommends continuing trastuzumab therapy for up to 1 year.

Results of small phase II trials indicate that other HER2-targeting agents such as lapatinib and pertuzumab have a clinical benefit in IBC.[269,688] The results of the NEOSPHERE trial that included patients with IBC showed increased pCR with the pertuzumab-containing regimens. Therefore, the NCCN Panel has included in a footnote that a pertuzumab-containing regimen may be administered preoperatively in patients with HER2-positive IBC.[269]

Determination of response to neoadjuvant chemotherapy in IBC should include a combination of physical examination and radiologic assessment.

Surgery

Patients with a clinical/pathologic diagnosis of IBC should always be treated with chemotherapy before surgery. It has been known for many years that surgical treatment as *primary* treatment of patients with IBC is associated with poor outcomes.[689] SLN dissection is not a reliable method of assessing ALNs among women with IBC.[690] Use of breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that rates of local recurrence may be higher when compared with mastectomy. Breast-conserving therapy is not recommended for patients with IBC.

Mastectomy with level I/II ALN dissection is the recommended surgical procedure recommended by the NCCN Panel for patients who respond to neoadjuvant chemotherapy. The NCCN Panel has listed delayed breast reconstruction as an option that can be recommended to women with IBC who have undergone a modified radical mastectomy. Reconstruction of the breasts soon after mastectomy may compromise the post-mastectomy radiation therapy outcomes.[691]

For patients with IBC who *do not* respond to preoperative systemic therapy, mastectomy is not generally recommended. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients. Patients with tumors responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above.

Radiation

After mastectomy, radiation therapy is recommended after the completion of the planned chemotherapy.

The probability of locoregional lymph node involvement is high for women with IBC. To reduce the risk of local recurrence, the panel recommends radiation therapy to the chest wall and the supraclavicular region. If the internal mammary lymph node(s) is clinically or pathologically involved, radiation therapy should include the internal mammary nodes. If the internal mammary nodes are not clinically or pathologically involved, then including the internal mammary nodes in the radiation therapy field is at the discretion of the treating radiation oncologist (category 3). For HER2-positive disease, trastuzumab may be administered concomitantly with radiation therapy.

Stage IV or Recurrent IBC

Patients with stage IV or recurrent IBC should be treated according to the guidelines for recurrence/stage IV breast cancer (See NCCN Guidelines for Breast Cancer).

Axillary Breast Cancer

Occult breast cancer presenting with axillary metastases is an unusual presentation that can be a diagnostic and therapeutic challenge. Evidence to support recommendations on the management of patients presenting with axillary breast cancer comes from a limited number of retrospective studies involving small numbers of patients[692-694](see also references therein). Although treatment of women with axillary metastases from an unknown primary tumor has typically involved mastectomy and axillary nodal dissection, some of these patients have also been successfully treated with axillary nodal dissection followed by radiation therapy.[693,694]

Patients with a suspected occult primary breast cancer will typically present to the oncologist after undergoing an initial biopsy: core needle biopsy (preferred), and/or FNA. Accurate pathologic assessment of the biopsied material is most important. Therefore, the pathologist must be consulted to determine whether the available biopsy material is adequate, or if additional biopsy material is necessary (eg, core needle, incisional, or excisional biopsy) to provide an accurate and complete diagnosis.

Workup for Possible Primary Breast Cancer

MRI of the breast can facilitate the identification of occult breast cancer, and can help select those patients most likely to benefit from mastectomy.[695] For example, in a study of 40 patients with biopsy-proven breast cancer in the axilla, and a negative or indeterminate mammogram, MRI identified the primary breast lesion in 70% of the patients.[693] In addition, of the 7 patients with a negative MRI who subsequently underwent ALN dissection and radiation therapy to the whole breast, no evidence of local recurrence was evident at a median follow-up of 19 months.

The NCCN Guidelines for Occult Primary Cancer provide guidance on the diagnosis and initial workup of patients with a suspicious axillary mass without any signs of a primary tumor. A small subset of these patients may have a primary cancer in the axillary tail of the breast. Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Adenocarcinoma in the supraclavicular nodes, chest, peritoneum, retroperitoneum, liver, bone, or brain could also indicate primary breast cancer in women. The guidelines suggest the use of a mammogram and breast ultrasound for such patients.

Testing for immunohistochemical markers including ER/PR and HER2 is recommended. Elevated ER/PR levels provide strong evidence for a breast cancer diagnosis.[696] MRI of the breast should be considered for a patient with histopathologic evidence of breast cancer when mammography and ultrasound are not adequate to assess the extent of the disease. MRI may be especially helpful in women with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor or to evaluate the chest wall.[697] Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer and may also facilitate breast conservation in selected women by allowing for lumpectomy instead of mastectomy.[693,698] In one report, the primary site was identified using MRI in about half of the women presenting with axillary metastases, irrespective of the breast density.[699]

The NCCN Guidelines for Occult Primary Cancer also provide recommendations for additional workup, including chest and abdominal CT to evaluate for evidence of distant metastases for patients diagnosed with adenocarcinoma (or carcinoma not otherwise specified) of the axillary nodes without evidence of a primary breast lesion. In particular, breast MRI and ultrasound are recommended. Axillary ultrasound should also be performed.

Treatment for Possible Primary Breast Cancer

Patients with MRI-positive breast disease should undergo evaluation with ultrasound or MRI-guided biopsy and receive treatment according to the clinical stage of the breast cancer. Treatment recommendations for those with MRI-negative disease are based on nodal status. For patients with T0, N1, M0 disease, options include mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation. Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for stage II or III disease. Neoadjuvant chemotherapy, trastuzumab, and endocrine therapy should be considered for patients with T0, N2-N3, M0 disease followed by axillary nodal dissection and mastectomy as for patients with locally advanced disease.

Summary

The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. In many situations, the patient and physician have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. With few exceptions, the evaluation, treatment, and follow-up recommendations in these guidelines are based on the results of past and present clinical trials. However, there is not a single clinical situation in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. Therefore, patient/physician participation in prospective clinical trials allows patients to not only receive state-of-the-art cancer treatment but also to contribute to improving the treatment outcomes.

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