National Comprehensive Cancer Network®

NCCN.org

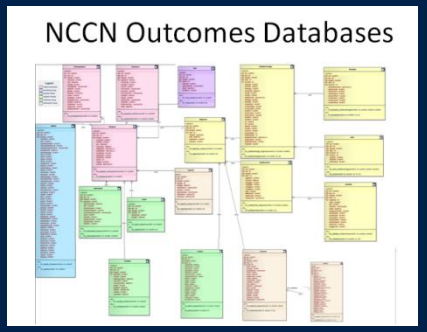
NCCN National Comprehensive Cancer Network®

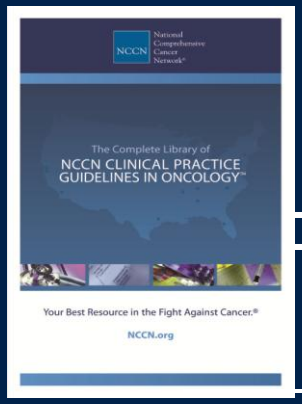
What is NCCN?

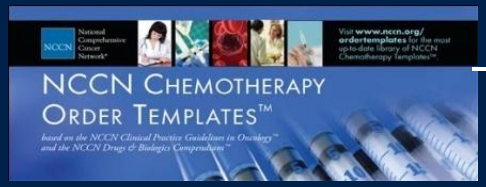
- Arbiter of high-quality cancer care
- Developer and Promoter of National Programs to facilitate the fulfillment of member institution missions in education, research, and patient care and to incrementally advantage NCCN institutions in the marketplace
- Developer and Communicator of scientific, evaluative information to better inform the decision-making process between patients and physicians, ultimately improving patient outcomes
- Seek to enhance the effectiveness and efficiency of cancer care through information resources, outcomes research, clinical trials, and other contributions to the cancer care delivery system

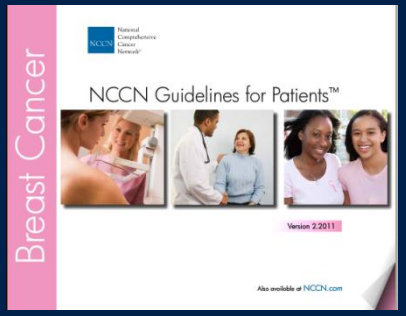
© NCCN All rights reserved.

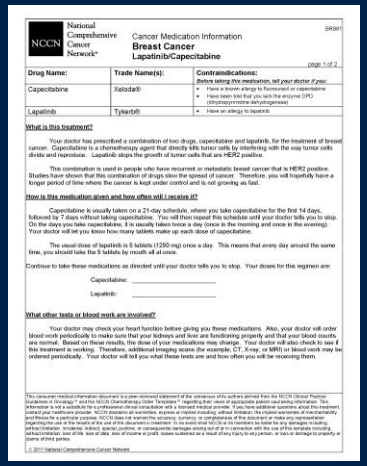
Integrated Suite of NCCN Information Products











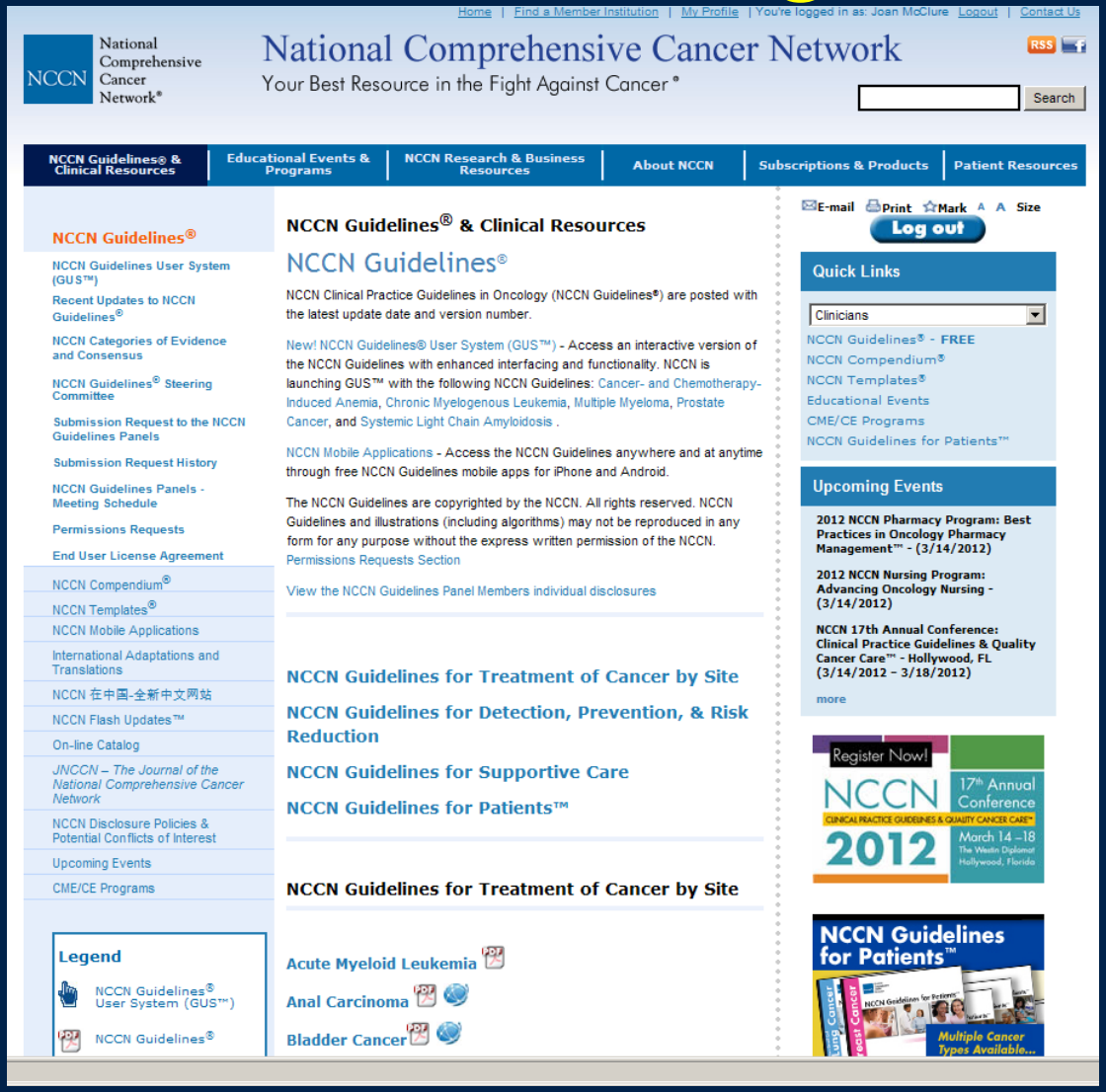
© NCCN All rights reserved

NCCN Guidelines™

- Comprehensive across all stages, modalities and continuum of care
  - 47 multidisciplinary expert panels with 25-30 experts per panel (Volunteer time and expertise)
  - Cancer screening, diagnosis, treatment and supportive care
- Updated at least annually and up to 4 times per year since 1995
- Category of evidence and consensus designated for each recommendation
- Transparent processes
- Centerpiece of suite of tools to support quality oncology care

© NCCN All rights reserved.

Guidelines Available on NCCN.org



Parts of a Guideline

- Panel list
- Table of Contents
- Algorithms including special topics
- Discussion
- References

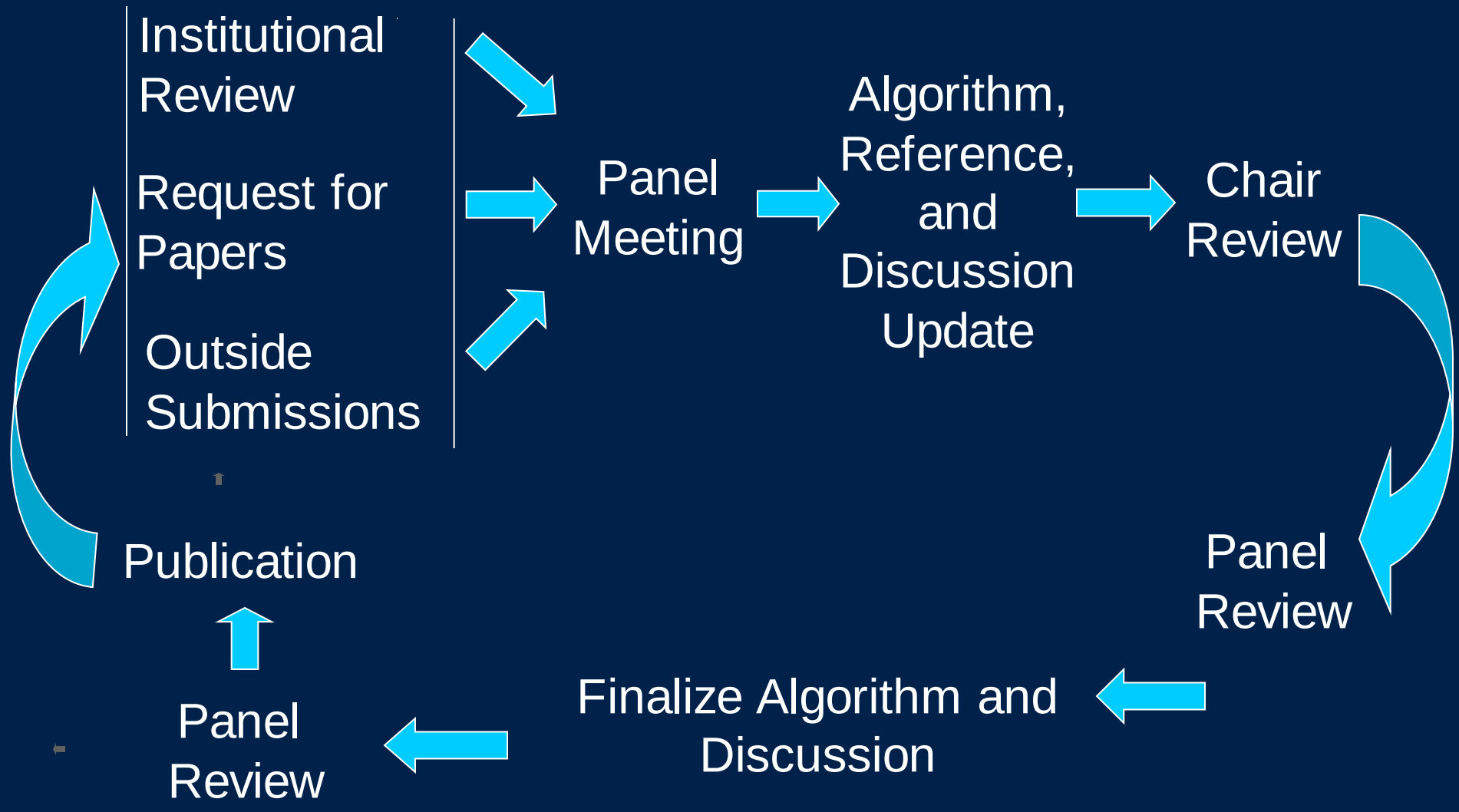
© NCCN All rights reserved.

Who Develops Guidelines

- Faculty from Member Institutions
  - Multidisciplinary
  - Volunteers
  - Mix of senior, mid-career, and junior faculty
- NCCN Staff Support
  - Oncology scientist
  - Guidelines coordinator
  - Administrative assistants

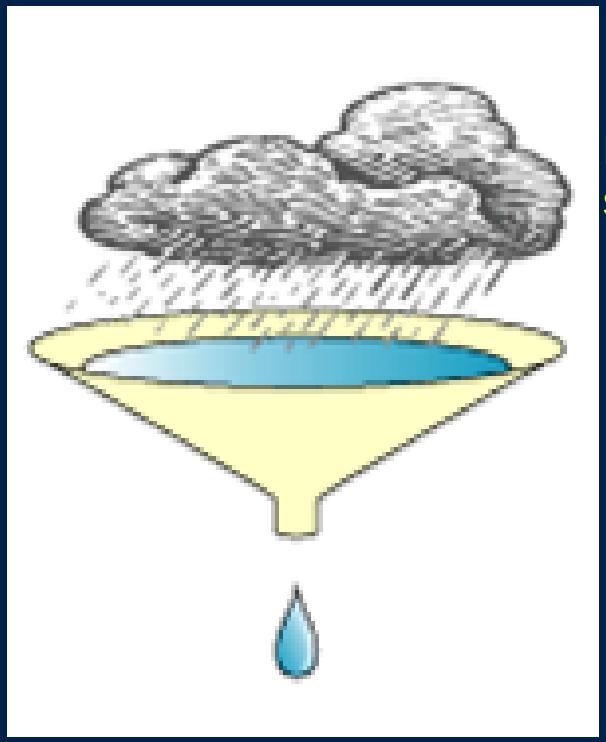
© NCCN All rights reserved.

Guideline Update Process: Continuous Improvement



© NCCN All rights reserved.

Evidence



Data from multiple studies and sources

↓

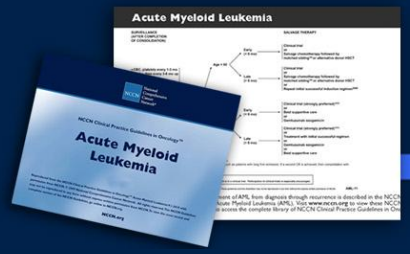
Expert evaluation

↓

Distill appropriate recommendations

- **Ongoing process**
- **The amount of data available differs across disease sites and across clinical decisions within a disease site**
- **Continuous review of evidence and guideline updates is required**
- **New studies WILL change the standard of care over time**

© NCCN All rights reserved.



NCCN Guidelines®

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 All rights reserved.

Critical Analysis and Culling of Data

- NCCN Categories of Evidence
  - 1, 2A, 2B, 3
- Consistency of evidence
  - Highly consistent, single trial, variable data
- Extent of evidence
  - Extensive, less extensive, little, clinical experience
- Quality of evidence
  - Meta analysis/systematic review, RTCs, nonRTCs, clinical experience

© NCCN All rights reserved.

Melding Evidence with Expertise

- While data are objective, application of data is not
- Clinical judgement is always subjective
- The specified cutoffs for treatment or no treatment, testing or no testing, the weighing of risk versus benefit reflect the values and preferences of the experts who write the recommendations.

Pamela Hartzband, M.D., and Jerome Groopman, M.D N ENGL J MED 2011; 365:1372-1373

© NCCN All rights reserved.

Making Recommendations

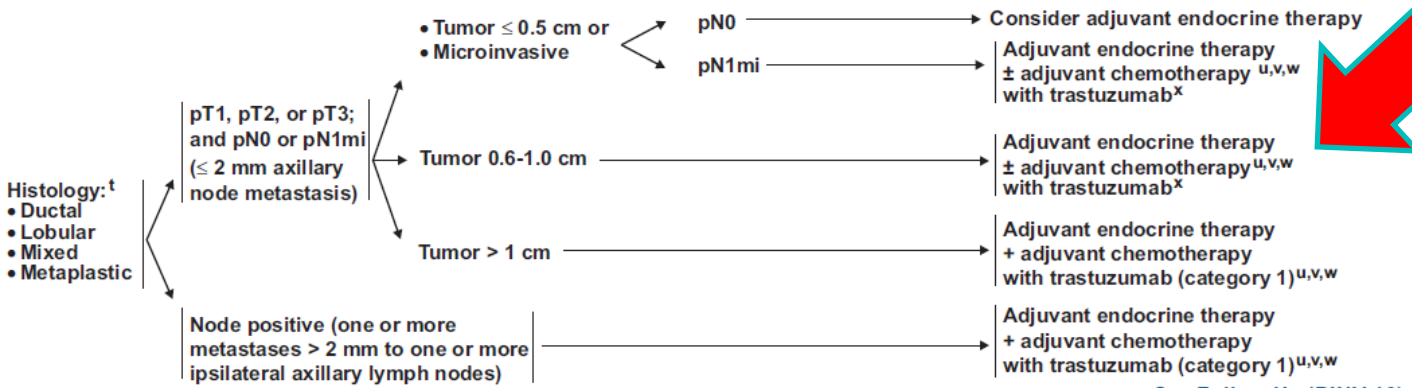
Printed by Joan McClure on 4/11/2012 3:54:10 PM. For personal use only. Not approved for distribution. Copyright © 2012 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2012
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Staging, Discussion

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 POSITIVE DISEASE[b]



See Follow-Up (BINV-16)
See Adjuvant Endocrine Therapy (BINV-J) and Adjuvant Chemotherapy (BINV-K)

[b] See Principles of HER2 Testing (BINV-A).

[t] Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[u] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

[v] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. The benefits of chemotherapy and of endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to endocrine therapy should be individualized, especially in those with a favorable prognosis where the incremental benefit of chemotherapy may be smaller. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[w] There are limited data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

[x] The prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2012, 01/20/12 © National Comprehensive Cancer Network, Inc. 2012, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

The Universe of Data

PubMed Clinical Queries

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

Breast neoplasms AND adjuvant therapy AND trastuzumab | Search

Clinical Study Categories

Category: Therapy

Scope: Broad

Results: 5 of 767

Adjuvant trastuzumab in HER2-positive breast cancer. [N Engl J Med. 2011]

[Appearance of skin and nail toxicity in patients with breast cancer who underwent trastuzumab-containing chemotherapy]. [Gan To Kagaku Ryoho. 2011]

Elucidating an uncommon disease: inflammatory breast cancer. [J Natl Cancer Inst. 2011]

Pathological complete response and prognosis in patients receiving neoadjuvant paclitaxel and trastuzumab with and without anthracyclines for stage II and III, [Anticancer Res. 2011]

Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herce| [Eur J Surg Oncol. 2011]

See all (767)

Display citations filtered to a specific clinical study category and scope. These search filters were developed by Haynes RB et al. See more filter information.

Systematic Reviews

Results: 5 of 58

[Node negative breast cancer. Beyond international consensus: a pragmatic approach]. [Bull Cancer. 2011]

Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. [PLoS One. 2011]

Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer reg [Cancer. 2011]

[Cardiac safety of trastuzumab in adjuvant: a review across 53 observations]. [J Gynecol Obstet Biol Reprod (Paris). 2011]

Cardiac toxicity of trastuzumab: experience at the Ghent Unversity Hospital, Belgium. [Acta Clin Belg. 2010]

See all (58)

Display citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. See filter information or additional related sources.

Medical Genetics

Topic: All

Results: 5 of 182

Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herce| [Eur J Surg Oncol. 2011]

[Node negative breast cancer. Beyond international consensus: a pragmatic approach]. [Bull Cancer. 2011]

Genomic testing and therapies for breast cancer in clinical practice. [Am J Manag Care. 2011]

Management and outcome of HER2-positive early breast cancer treated with or without trastuzumab in the adjuvant trastuzumab era. [Clin Breast Cancer. 2011]

Adjuvant effect of HER-2/neu-specific adenoviral vector stimulating $CD8^+$ T and natural killer cell responses on anti-HER-2/neu antibody therapy for well-e [Cancer Gene Ther. 2011]

See all (182)

Display citations pertaining to topics in medical genetics. See more filter information.

Narrower Scope

PubMed Clinical Queries

Results of searches on this page are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

Breast neoplasms AND adjuvant therapy AND trastuzumab AND hormone receptor positive

Search

Clinical Study Categories

Category: Therapy

Scope: Broad

Results: 5 of 53

Hormonal therapy plus bevacizumab in postmenopausal patients who have hormone receptor-positive metastatic breast cancer: a phase II Trial of the Sarah ([Clin Breast Cancer. 2011]

Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer reg [Cancer. 2011]

Early breast cancer in the older woman. [Oncologist. 2011]

Lapatinib in breast cancer: clinical experiences and future perspectives. [Cancer Treat Rev. 2010]

Semiquantitative hormone receptor level influences response to trastuzumab-containing neoadjuvant chemotherapy in HER2-positive breast cancer. [Mod Pathol. 2011]

See all (53)

Display citations filtered to a specific clinical study category and scope. These search filters were developed by Haynes RB et al. See more filter information.

Systematic Reviews

Results: 4 of 4

Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer reg [Cancer. 2011]

Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. [Breast Cancer Res Treat. 2011]

Current standards in the treatment of metastatic breast cancer with focus on Lapatinib: a review by a Central European Consensus Panel. [Wien Klin Wochenschr. 2010]

Overview of resistance to systemic therapy in patients with breast cancer. [Adv Exp Med Biol. 2007]

See all (4)

Display citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines. See filter information or additional related sources.

Medical Genetics

Topic: All

Results: 5 of 8

Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer reg [Cancer. 2011]

Multigene assays and isolated tumor cells for early breast cancer treatment: time for bionetworks. [Expert Rev Anticancer Ther. 2010]

HER2 and chromosome 17 effect on patient outcome in the N9831 adjuvant trastuzumab trial. [J Clin Oncol. 2010]

Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced b [Lancet. 2010]

Hormone receptor status and pathologic response of HER2-positive breast cancer treated with neoadjuvant chemotherapy and trastuzumab. [Ann Oncol. 2008]

See all (8)

Display citations pertaining to topics in medical genetics. See more filter information.

© NCCN All rights reserved.

Panels' Clinical Trials Evaluation

- Patient cohort—staging, markers, comorbid conditions, prior therapy, demographics, etc.
- Statistical plan—appropriate, planned analyses
- Appropriate comparator
- Dose, dose adjustments, reporting and management of AEs, etc
- Response assessment methods and consistency
- Analysis of results

© NCCN All rights reserved.

Use Seminal References

- 1007 citations on adjuvant therapy for HER2 overexpressed breast cancer in PubMed
- NCCN panel judged 11 published papers and 3 abstracts from professional meetings persuasive
- These references are included in the guidelines with links to abstracts

© NCCN All rights reserved.

Therapeutic Index

- Each recommendation is considered in light of both safety and efficacy
- In adjuvant setting, safety and efficacy are equally weighted
- In potentially curative situation, more toxicity is tolerated for good efficacy
- In palliative setting, less toxicity is acceptable

© NCCN All rights reserved.

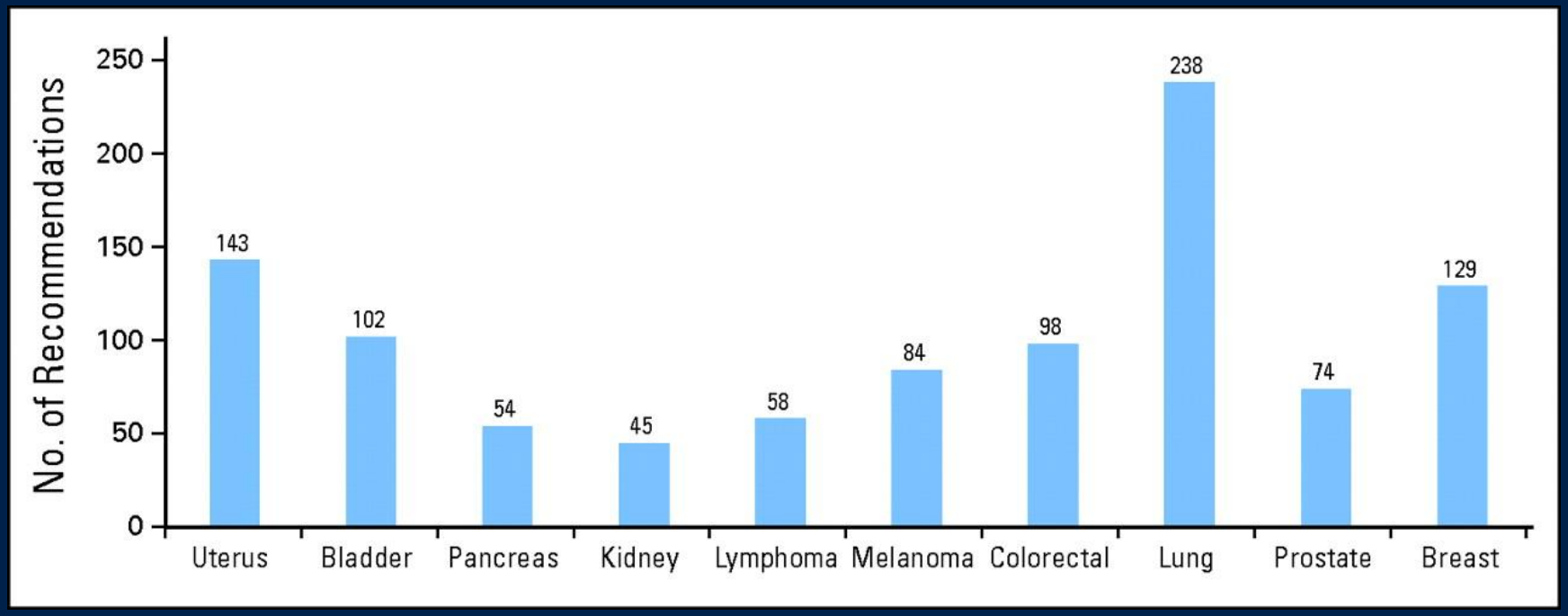
Citations Across Guidelines

Preliminary Data

In general:

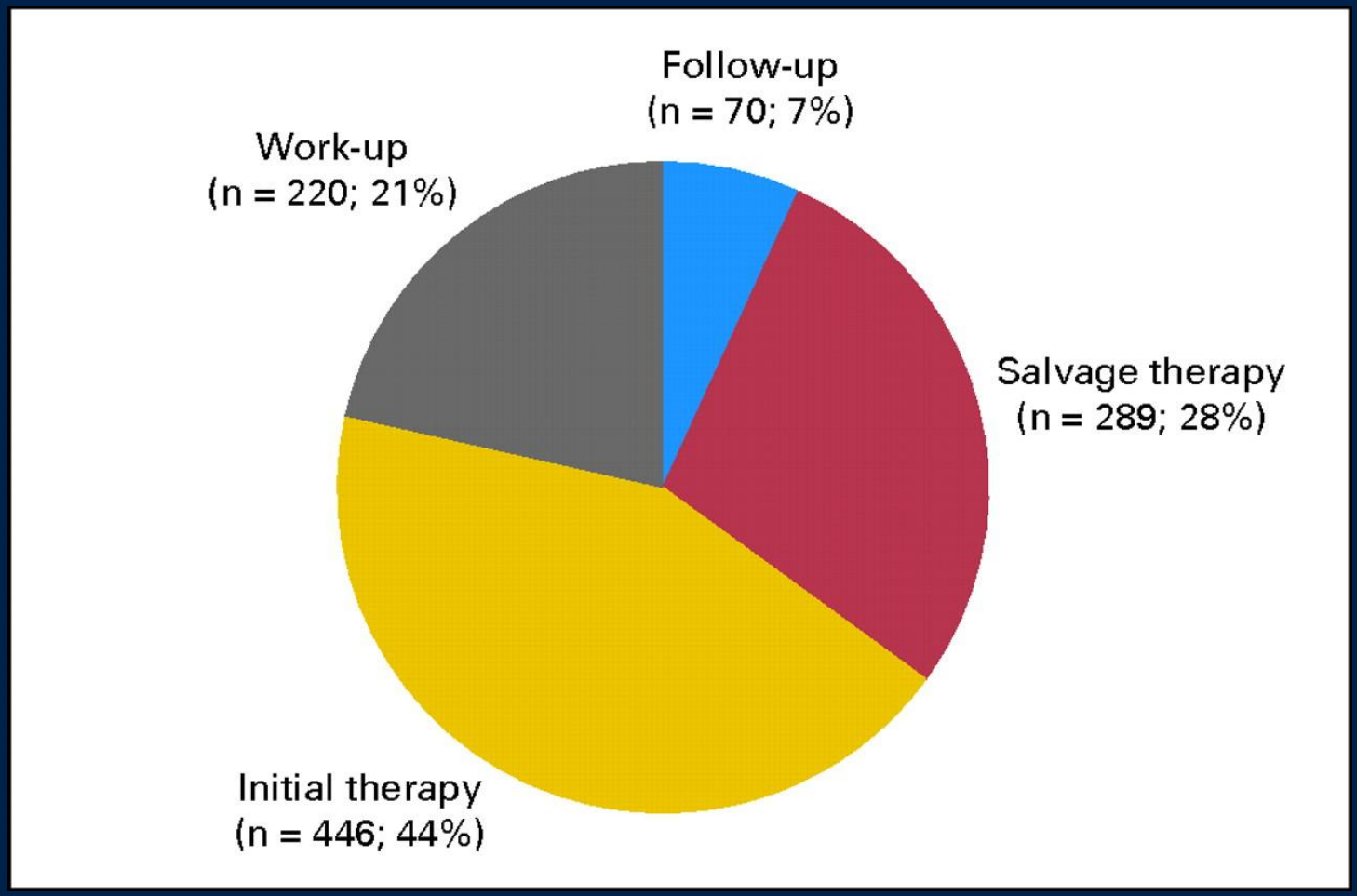
- More references:
  - Large complicated guidelines
  - Large numbers of patients
  - High priority cancers
- Fewer references
  - Lower incidence
  - Few innovations
  - Fewer effective interventions

Recommendations per Guideline



Poonacha T K , Go R S JCO 2011;29:186-191

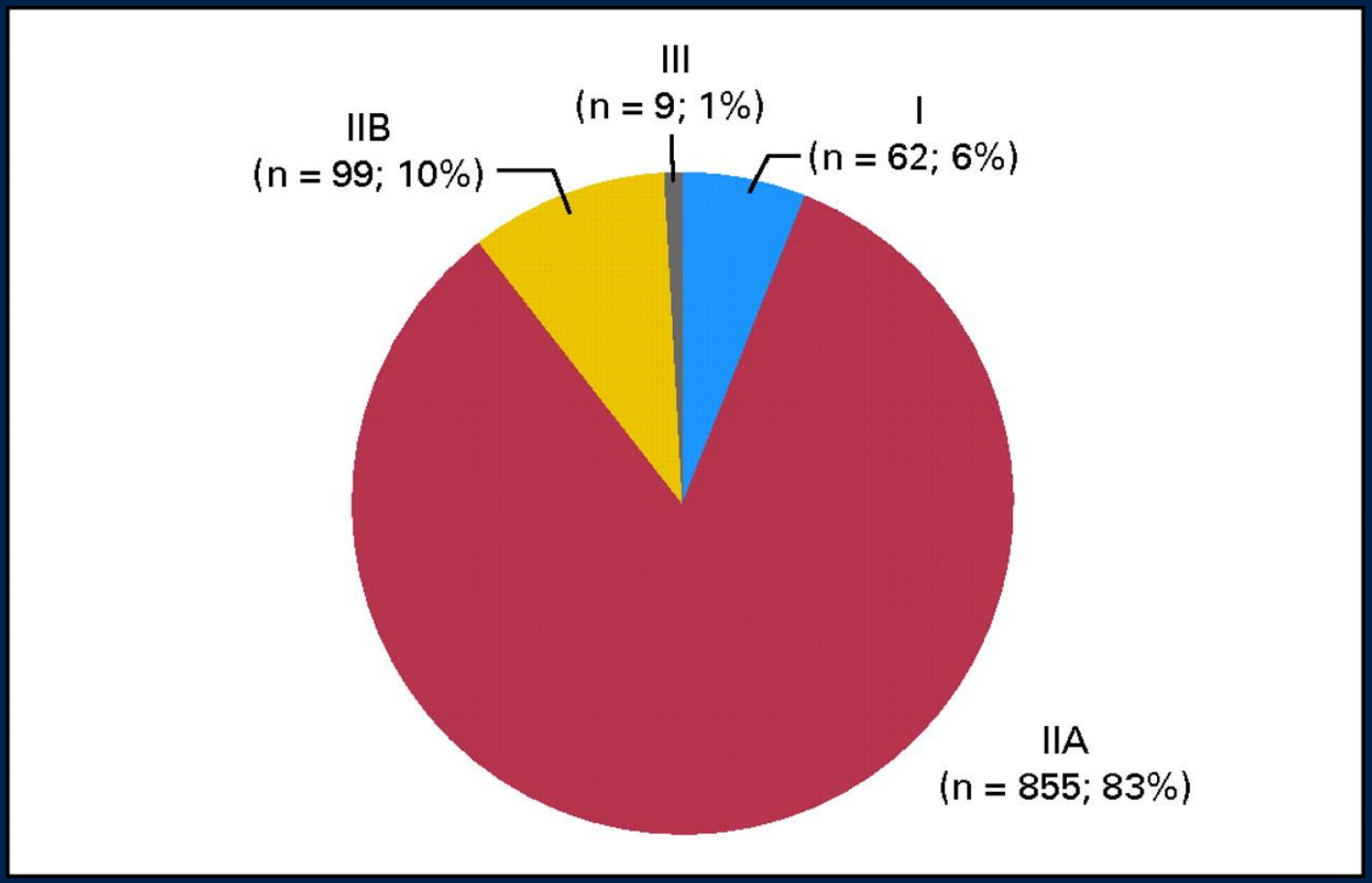
Types of Recommendations



Poonacha T K , Go R S JCO 2011;29:186-191

© NCCN All rights reserved.

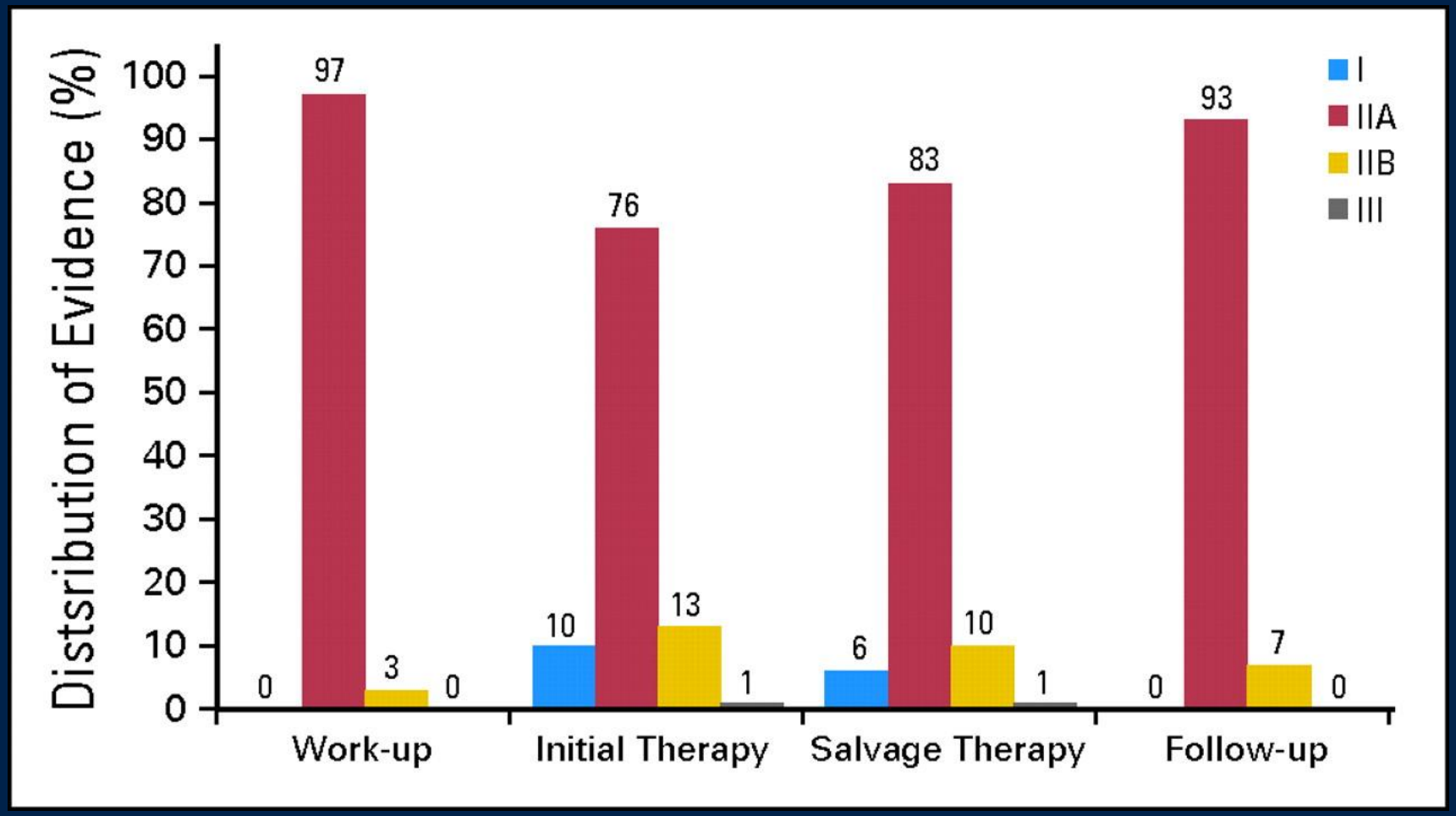
Recommendations by Evidence Category



Poonacha T K , Go R S JCO 2011;29:186-191

© NCCN All rights reserved.

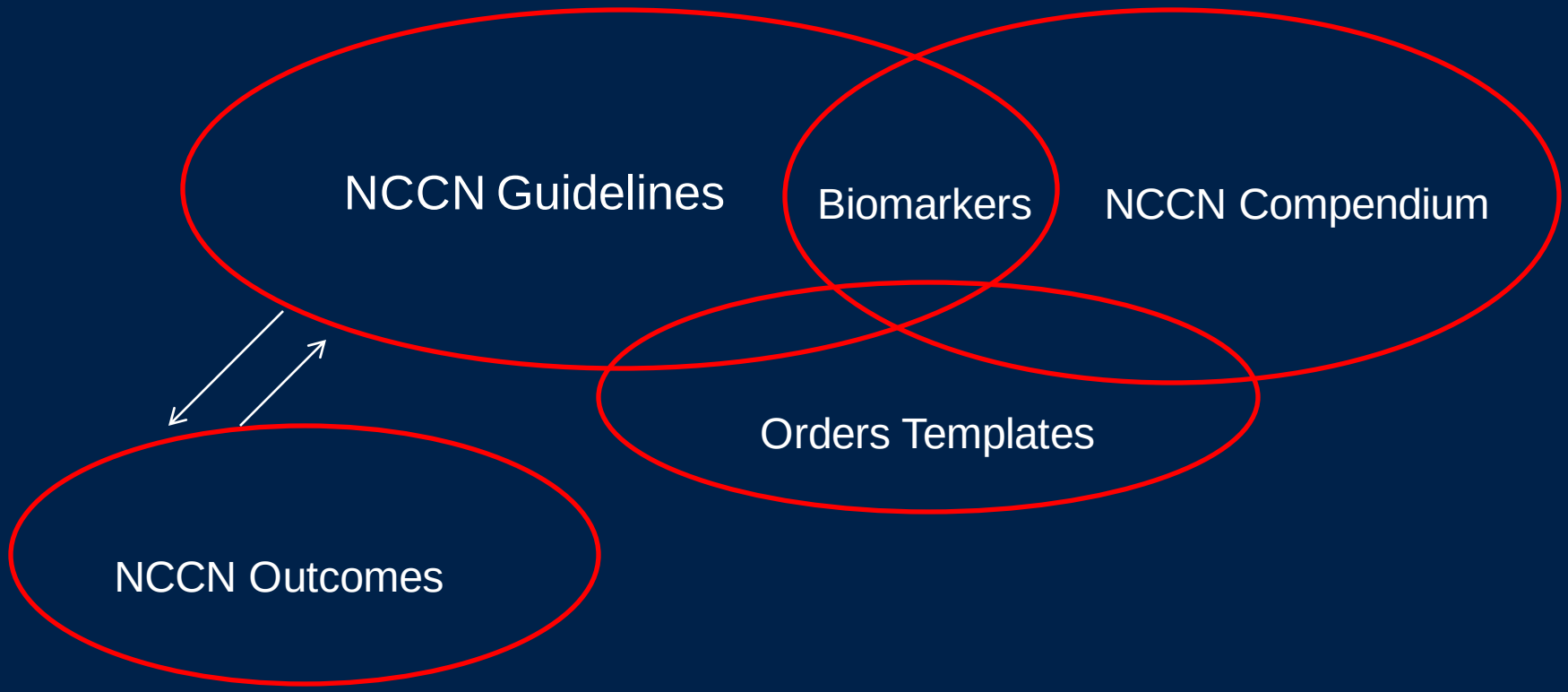
Evidence by Type of Recommendation



Poonacha T K , Go R S JCO 2011;29:186-191

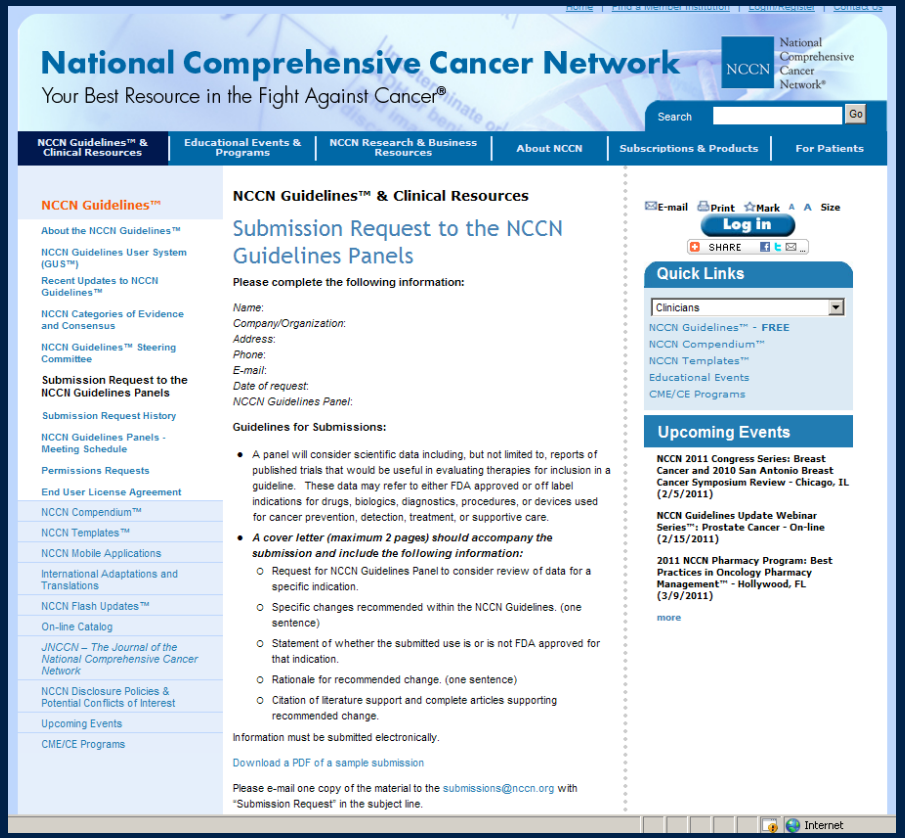
© NCCN All rights reserved.

Content Relationships



© NCCN All rights reserved.

Submitting Data to NCCN Panels



- Submissions from community sites, industry, payers, and the advocacy community
- The quality of the data is paramount
- Data submitted to the NCCN (not to individual panel members)
- Panel members interpret the data using their expert judgement

© NCCN All rights reserved.

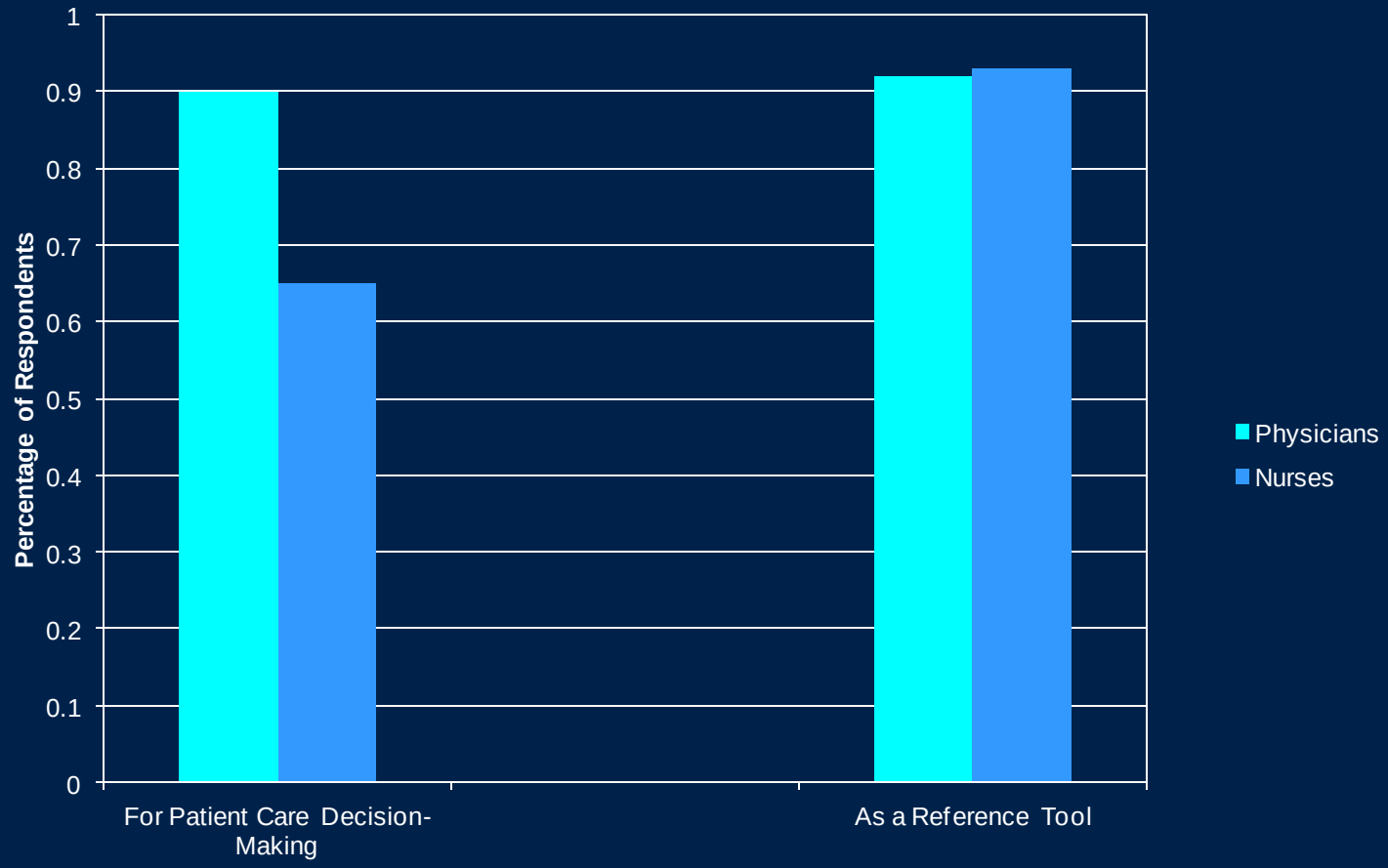
Disclosure

- No industry or any other interest group funds are used to support panel meetings
- No industry representatives allowed at meetings
- Individual panel members disclose conflicts of interest at least annually
- Specific limits on financial relationships
- Financial conflicts of interest published for individuals on nccn.org.
- Members are excused from deliberations when degree of conflict warrants

© NCCN All rights reserved.

Guidelines Implementation

Clinicians Use NCCN Guidelines for Patient Care Decision-Making and As a Reference Tool (n= 1,861)



© NCCN All rights reserved.

Challenges in Implementation of Guidelines

- Guideline distribution is not enough
- Education alone is not adequate to change practice
- Disease site guidelines are more readily adopted

© NCCN All rights reserved.

Strategies to Encourage Implementation

- Coverage policy can encourage adoption
- Incorporation in clinical support tools can help
- Benchmarking concordance against standard increases awareness
- Patient reported outcomes of own patients can improve adoption

© NCCN All rights reserved.

NCCN Guidelines for Patients™

© NCCN All rights reserved.

NCCN Guidelines for Patients™

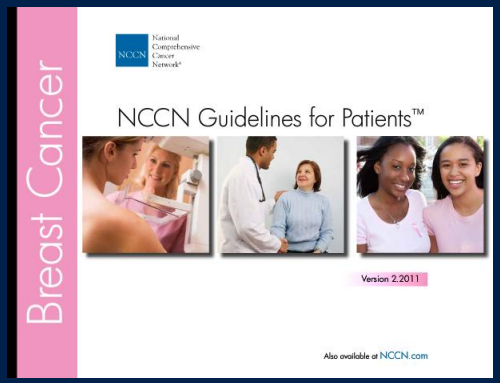


Table 6. Chemotherapy regimens for recurrent or metastatic breast cancer

Preferred agents	Preferred combinations
Doxorubicin	CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
Epirubicin	FEC (fluorouracil/epirubicin/cyclophosphamide)
Pegylated liposomal doxorubicin	AC (doxorubicin/cyclophosphamide)
Paclitaxel	AT (doxorubicin/docetaxel or doxorubicin/paclitaxel)
Docetaxel	CMF (cyclophosphamide/methotrexate/fluorouracil)
Albumin-bound paclitaxel	Docetaxel/capecitabine
Capecitabine	GT (gemcitabine/paclitaxel)
Gemcitabine	**Other combinations**
Vinorelbine	Ixabepilone and capecitabine
Eribulin	**Preferred agents for HER2-positive tumors**
Paclitaxel with bevacizumab	Trastuzumab and paclitaxel with or without carboplatin
Other agents	Trastuzumab and docetaxel
Cisplatin	Trastuzumab and vinorelbine
Carboplatin	Trastuzumab and capecitabine
Cyclophosphamide	**Preferred agents for trastuzumab-treated HER2-positive tumors**
Mitoxantrone	Lapatinib and capecitabine
	Trastuzumab with different chemotherapy drug than was used before
	Trastuzumab and capecitabine
	Trastuzumab and lapatinib (with no other chemotherapy)

HER2 positive and hormone negative/refractory

Spread of cancer	Treatment
	Denosumab or bisphosphonate if bone metastases
Bone or soft tissue only or no symptoms of spread	Consider different hormone therapy unless no response to 2 or 3 back-to-back therapies
	Trastuzumab with or without chemotherapy
Symptoms of cancer in internal organs	Trastuzumab with or without chemotherapy

Trastuzumab with or without chemotherapy → Use different chemotherapy or trastuzumab with lapatinib → Consider supportive care only if no response to three regimens or in poor general health

For hormone therapy, see the next chart.
For follow-up hormone therapy, see Part 7.7.5.

This chart is for women with tumors that are HER2-positive and hormone receptor—negative or that have not responded to hormone therapy. Hormone therapy may be given if your cancer has spread only to the bones or soft tissues, or your cancer has spread to other organs that are still working well. Otherwise, since the tumor is HER2 positive, trastuzumab may be given either alone or with chemotherapy. If your cancer still grows, trastuzumab may be continued with a different chemotherapy drug. Another choice is to try a combination of lapatinib with more trastuzumab or with another chemotherapy drug. If the tumor does not shrink after three different chemotherapy regimens, stopping chemotherapy and receiving supportive care may be your best option. If you have bone metastases, treat dental problems first before taking bisphosphonate or denosumab.

© NCCN All rights reserved.

How is DCIS First Suspected?

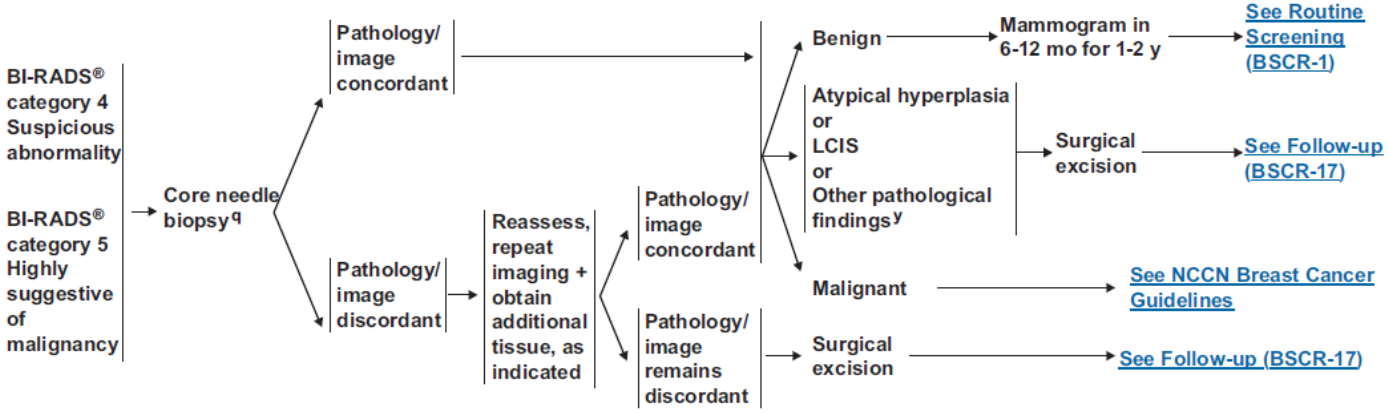
- Most often by screening mammography
- Rarely a lump is felt by the woman or the clinician
- Which type of physician interacts with the patient at which stage varies
  - Primary care physician
  - Gynecologist
  - Diagnostic radiologist
  - Interventional radiologist
  - Surgeon

© NCCN All rights reserved.

Followup of Abnormal Mammogram

Printed by Joan McClure on 4/6/2012 10:48:03 AM. For personal use only. Not approved for distribution. Copyright © 2012 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ASSESSMENT CATEGORY[j,k] **DIAGNOSTIC MAMMOGRAM FOLLOW-UP**

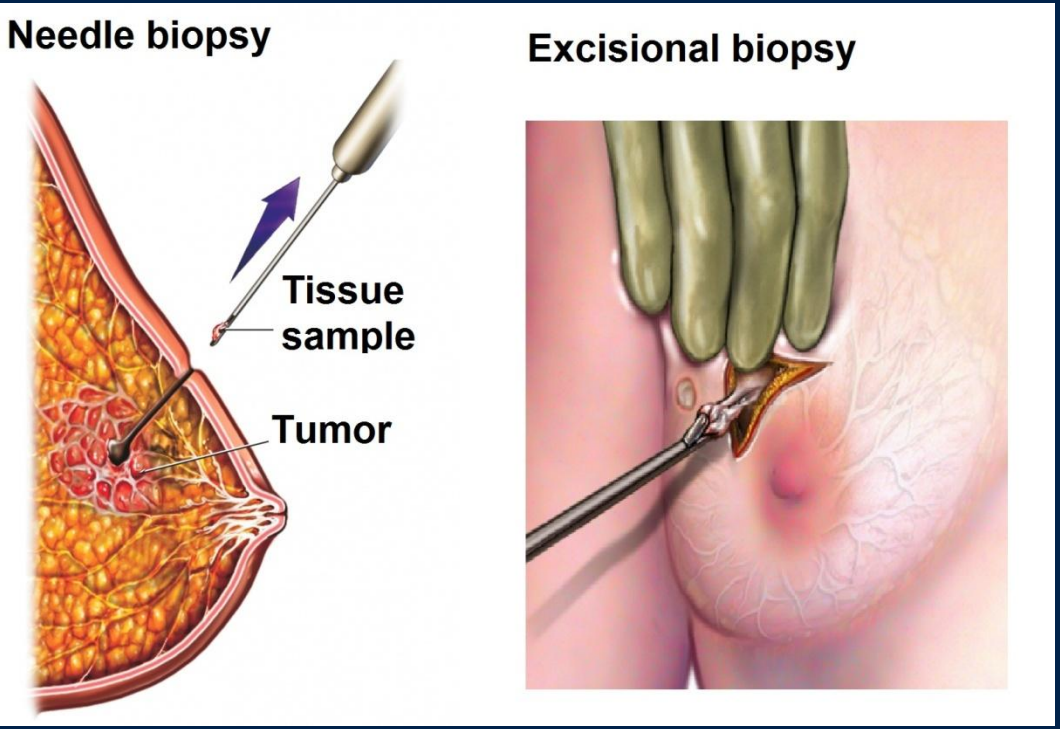


[j] See Mammographic Assessment Category Definitions (BSCR-C).
[k] Mammography results are mandated to be reported using Final Assessment categories (Mammography Quality Standards Act, Final Rule. Federal Register 62(208):55988, 1997).
[q] FNA and core (needle or vacuum-assisted) biopsy are both valuable. FNA requires cytologic expertise.
[y] Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar or other histologies of concern to pathologist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2011, 11/19/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Biopsy Techniques



Needle Biopsy	Excisional Biopsy
Fewer trips to the operating room	Inadequate or indeterminate needle biopsy
Can sample multiple abnormal areas	Additional tissue needed for pathology review

Needle Biopsies

- FNA: Smaller-bore needle, minimally invasive, low cost, but requires specialized pathologist and may need second core biopsy
- Core Needle Biopsy: Large-bore cutting needle removes 3-5 cores. Can obtain large enough tissue samples for diagnosis. Can place clip to guide further treatment
- Image guided core needle biopsy: Uses ultrasound or mammography to guide sampling

© NCCN All rights reserved.

NCCN Database: Rates of Needle vs Excisional Biopsy

Initial Biopsy	N	%
FNA	2	0%
Needle-Non Image Guided	40	5%
Needle-Image Guided	567	77%
Surgical-Non Image Guided	64	9%
Surgery-Image Guided	64	9%

Clinical Stage 0
Diagnosed January—December 2010
>90 days follow-up
Community and Academic Centers' rates are similar

©NCCN All rights reserved.

National Comprehensive Cancer Network®

NCCN.org