Neoadjuvant Therapy for Breast Cancer

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Introduction

Globally

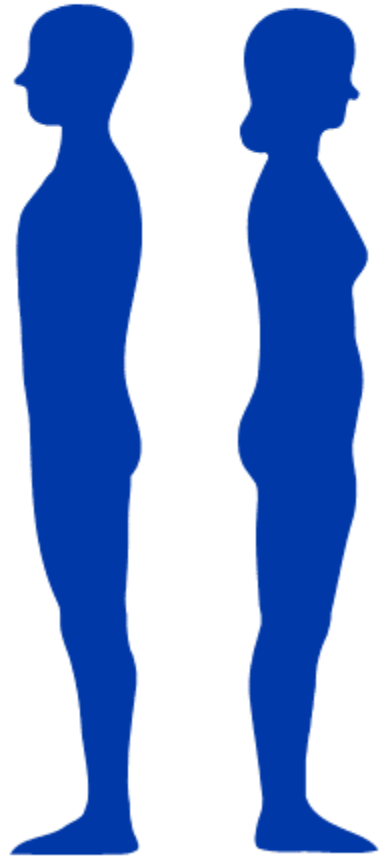
- Breast cancer: the most frequently diagnosed cancer
- Leading cause of cancer death in women

In the United States

- Breast cancer: the most commonly diagnosed cancer
- Second most common cause of cancer death in women
- In addition, the leading cause of death in women ages 40 to 49 years

Estimated New Cancer Cases* in the US in 2018

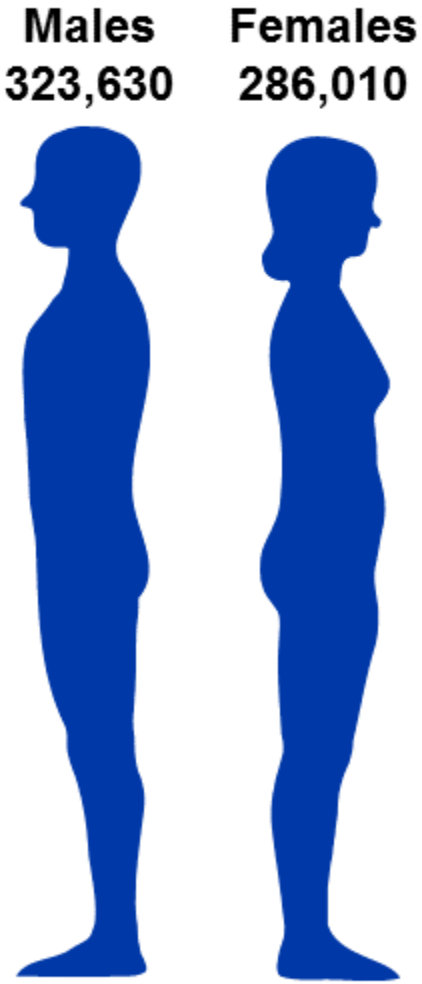
Males 856,370	
Prostate	19%
Lung & bronchus	14%
Colon & rectum	9%
Urinary bladder	7%
Melanoma of skin	6%
Kidney & renal pelvis	5%
Non-Hodgkin lymphoma	5%
Oral cavity & pharynx	4%
Leukemia	4%
Liver & intrahepatic bile duct	4%
All other sites	22%



Females 878,980	
30%	Breast
13%	Lung & bronchus
7%	Colon & rectum
7%	Uterine corpus
5%	Thyroid
4%	Melanoma of skin
4%	Non-Hodgkin lymphoma
3%	Pancreas
3%	Leukemia
3%	Kidney & renal pelvis
21%	All other sites

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Estimated Cancer Deaths in the US in 2018



Males 323,630		Females 286,010	
Lung & bronchus	26%	25%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	8%	8%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	6%	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	4%	4%	Leukemia
Urinary bladder	4%	3%	Liver & intrahepatic bile duct
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
Kidney & renal pelvis	3%	3%	Brain & other nervous system
All other sites	24%	24%	All other sites

The Lifetime Probability of Developing Cancer for Females, 2012-2014

Site	Risk
All sites*	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 17
Colon & rectum	1 in 24
Uterine corpus	1 in 35
Melanoma of the skin†	1 in 42
Non-Hodgkin lymphoma	1 in 54
Thyroid	1 in 56
Pancreas	1 in 65
Ovary	1 in 78
Leukemia	1 in 80

*All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder. †Statistic for non-Hispanic whites.
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.5 Statistical Research and Applications Branch, National Cancer Institute, 2017.

Breast carcinoma TNM anatomic stage group AJCC UICC 2017

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

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Introduction

Non-metastatic breast cancer

- **Early stage** – Patients with stage I, IIA, or a subset of stage IIB disease (T2N1)
- **Locally advanced** – A subset of patients with stage IIB disease (T3N0) and stage IIIA to IIIC disease

Metastatic:

- 5% of patients: Metastatic disease identified at the initial presentation (de novo stage IV breast cancer)

General Principle of Treatment

Early stage or on-metastatic:

- Surgery (Lumpectomy or mastectomy)
- Adjuvant systemic therapy (chemo, hormonal)
- Adjuvant XRT
- **Neoadjuvant therapy (chemotherapy or hormonal)**

Metastatic disease:

Palliative therapy (chemotherapy, hormonal, targeted, immunotherapy or XRT

General principles of neoadjuvant therapy for breast cancer

Systemic treatment of breast cancer prior to definitive surgery (preoperative therapy)

Typically chemotherapy

Increasing interest in expanding the role of neoadjuvant endocrine therapy in certain subsets of patients

Goals

- Downstage the tumor, allowing for less extensive surgery
- Improved cosmetic outcomes
- Reduced postoperative complications such as lymphedema
- Permits an early evaluation of the effectiveness of systemic therapy
- The presence or absence of residual invasive cancer after neoadjuvant therapy: A strong prognostic factor for recurrence, especially in ER-negative and/or HER2-positive patients

Patient Selection

- **Locally advanced breast cancer** –stage IIB T3 disease to IIIC, often not amenable to upfront resection, much less breast conservation, and risk of recurrence warrants systemic chemotherapy
- **Select cases of early-stage breast cancer(**stage I or II): Appropriate if breast-conserving surgery not possible due to a high tumor-to-breast ratio, or postoperative cosmetic outcome suboptimal due to tumor location
- **Patients with even smaller (T1c):** Triple-negative or HER2-positive

    Need chemotherapy anyway

    Associated with a high likelihood of response

Patient Selection

- **Potential role of NACT:**
  - Early-stage breast cancer, regardless of the size of the primary tumor, to downstage the axillary nodes with limited node-positive disease (cN1)
  - The standard surgical approach for clinically node-positive breast cancer: Axillary lymph node dissection (ALND), associated with higher rates of lymphedema
  - Neoadjuvant chemotherapy shrinks nodal disease in cN1 patients
  - Results of contemporary studies: Such patients can be effectively treated with sentinel lymph node biopsy (SLNB) and regional nodal irradiation, with much lower rates of lymphedema

Patient Selection

- **Patients with temporary contraindications for surgery** –breast cancer during pregnancy

- **Inflammatory breast cancer:**

  Aggressive locally advanced breast cancer

  Lumpectomy and sentinel lymph node biopsy: Inappropriate even in the presence of a strong response to neoadjuvant therapy

  Multimodality approach: Chemotherapy followed by mastectomy, node dissection and postmastectomy radiation

Neoadjuvant chemotherapy versus adjuvant chemotherapy

- Multiple clinical trials: Neoadjuvant chemotherapy versus adjuvant chemotherapy
- A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group based upon data from 4756 women in 10 trials between 1983 and 2002
- Neoadjuvant chemotherapy:

  Increased frequency of breast-conserving therapy (65 versus 49 %)

  Increased risk of local recurrence (15-year local recurrence rate, 21.4 versus 15.9 %

  No difference in the risk of distant recurrence (15-year rate, 38.2 versus 38.0 %) or breast cancer mortality (34.4 versus 33.7 %)

Pretreatment Evaluation

- Tumor evaluation
  - Histopathologic confirmation
  - Evaluation of receptor status(ER,PR)
  - HER2 status
- Radiopaque clips placed in the tumor and lymph node
- The clips allow for confirmation:
  - The site of the tumor was removed
  - Pathologic assessment of the surgical specimen

Pretreatment Evaluation

- **Imaging**

  Ultrasound: Sufficient to document tumor size

  MRI:

    Helpful to evaluate disease extent

    Multicentric disease with dense breast tissue

    Presence of deep axillary and internal mammary nodes

    Invasion of the underlying chest wall

Pretreatment Evaluation

Node evaluation

- Physical exam on the axilla. Ultrasound-guided fine needle aspiration (FNA) or core needle biopsy (CNB) to confirm pathologic involvement
- No lymph nodes palpated, need axillary ultrasound
- Suspicious lymph node on ultrasound, FNA or CNB of the suspicious lymph node
- Positive sample: Allow more appropriate treatment planning, especially relating to surgical management of the axilla after NACT

Treatment Options

Chemotherapy

- Hormone receptor-positive disease:

  Chemotherapy remains the standard

  Endocrine therapy for certain subset of patients

- Chemotherapy, given with anti-HER2 targeted drugs if the tumor is HER2 positive
- Special considerations for **triple-negative disease**

Choice of Regimen

Commonly used regimens for HER2-negative patients

- Anthracycline-based: Doxorubicin and cyclophosphamide followed by a taxane (docetaxel or paclitaxel) (AC-T)
- Nonanthracycline-containing regimens: Docetaxel and cyclophosphamide (TC)

-Patients with cardiac disease, advanced age, cardiac risk factors such as hypertension and diabetes mellitus

Choice of Regimen

In HER2-negative patients:

- Four cycles of dose-dense (every two weeks) doxorubicin and cyclophosphamide followed by paclitaxel given either weekly for 12 weeks (AC/weekly T) or every two weeks for four cycles (AC/T)

- Four to six cycles of TC

Choice of Regimen in Her-2 positive patients

HER2-positive breast cancer (25%)

- Biologically more aggressive
- More sensitive to cytotoxic chemotherapy
- Higher pathologic complete response (pCR) to neoadjuvant chemotherapy
- Clinical trial results from the last few years: Newer HER2-targeted agents more effective

Choice of Regimen in Her-2 positive patients

- **Trastuzumab** (Herceptin):

  Monoclonal antibody binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2)

  Mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells

- **Pertuzumab** (Perjeta):

  Monoclonal antibody binds to a different epitope on HER2

  Inhibiting HER2 dimerization and blocking HER2 downstream signaling

  Blocking HER2:HER3 heterodimerization, a mechanism of resistance to trastuzumab

  Halting cell growth and initiating apoptosis

  Pertuzumab combined with trastuzumab, more complete inhibition of HER2 signaling

Choice of Regimen in Her-2 positive patients

- Pertuzumab: Antitumor activity in HER2-positive metastatic disease who progressed on trastuzumab
- Higher pCR rates: 55% for FEC-THP and 64% for TCHP
- Higher pCR means better EFS and OS ? Unknown
- In 2013, the FDA granted accelerated approval for the addition of **Pertuzumab** to NACT and trastuzumab for patients with HER2-positive locally advanced, inflammatory, or early-stage (either greater than 2 cm or node positive) breast cancer

Choice of Regimen in Her-2 positive patients

- TCH(P) – Docetaxel and carboplatin every three weeks for six cycles with concurrent trastuzumab, with or without pertuzumab
- wPCbH(P) – Weekly paclitaxel with carboplatin, administered either every three weeks or weekly, with concurrent trastuzumab, with or without pertuzumab, for 18 weeks.
- AC-TH(P) – Doxorubicin and cyclophosphamide (AC) every two or three weeks for four cycles, followed by paclitaxel, weekly for 12 weeks (wP), or docetaxel every three weeks for four cycles. Trastuzumab, weekly for 12 weeks or every three weeks for four cycles, is started concurrent with initiation of the taxane. If pertuzumab is added, it should also be started with the initiation of the taxane and given every three weeks for four cycles
- TH(P)-AC – The same treatments discussed above administered in the reverse order, which may cause less cardiotoxicity
- FEC/EC-TH(P) or TH(P)-FEC/EC – Fluorouracil, epirubicin, and cyclophosphamide (FEC) every three weeks for three to four cycles or epirubicin and cyclophosphamide (EC) every three weeks for four cycles **in Europe**

Choice of Regimen in Her-2 positive patients

- Patients with low-risk, stage I (T1N0):
  Weekly paclitaxel with trastuzumab for 12 weeks

- Combination of trastuzumab and pertuzumab for up to 24 weeks
  (with endocrine therapy for hormone receptor-positive disease)

Aerosphere Trial

Phase II Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation trial (NeoSphere)

- 417 HER2-positive patients
- 12 weeks of either four cycles of Docetaxel with Trastuzumb, Pertuzumab, or both, or the combination of trastuzumab and pertuzumab without docetaxel, then surgery
- After surgery, anthracycline-based adjuvant chemotherapy (those randomized to trastuzumab and Pertuzumab alone also received adjuvant docetaxel) and completed a year of treatment with Trastuzumab
- Docetaxel with Pertuzumab and Trastuzumab: Higher pCR rate (46%)
- Docetaxel with trastuzumab (29%) or just pertuzumab (24%)
- Pertuzumab and trastuzumab without docetaxel: pCR rate of 17%

TRYPHAENA Trial

Phase II Trastuzumab plus Pertuzumab in Neoadjuvant HER2-Positive Breast Cancer (TRYPHAENA) trial

- Over 200 women with HER2-positive breast cancer
- FEC followed by docetaxel, with trastuzumab and pertuzumab starting either concurrently with FEC (FECHP-THP) or upon initiation of docetaxel (FEC-THP); or to docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP)
- pCR rates: 56 and 55 % for FECHP-THP and FEC-THP, (failing to demonstrate a pCR benefit), and 64% for TCHP
- Incidence of febrile neutropenia: 18% in FECHP-THP, 9% with FEC-THP, and 17% with TCHP
- Grade >3 diarrhea occurred in 4%, 5%, and 12% in these groups
- Grade 3 anemia and thrombocytopenia: Rare except in patients with TCHP (17% and 12%)
- Cardiotoxicity comparable between the two groups receiving anthracycline-based treatment and slightly lower in the TCHP arm

Investigational approaches

- Lapatinib with chemotherapy

- HER2-targeted therapy without chemotherapy

  Transtuzumab and Pertuzumab

  Trastuzumab and Lapatinib with hormonal therapy

Investigational approaches

PAMELA study

- Trastuzumab **and** lapatinib **–** The largest reported trial of dual HER2-targeted neoadjuvant therapy without concurrent chemotherapy
- A multicenter phase II trial, 151 patients
- 18 weeks of lapatinib and trastuzumab, with concurrent endocrine therapy in HR-positive patients
- pCR breast: 30% (18% with HR-positive and **43% with HR-negative cancers**)

Triple-negative disease

- **Standard**: Anthracycline and taxane-based
- Addition of carboplatin to anthracycline and taxane-based regimens for TNBC: **Controversial**
- Some favor adding weekly carboplatin in locally advanced patients (those with tumors >3 cm, positive nodes, or stage III disease)
- Other do not incorporate carboplatin for TNBC in general, given its inconsistent effects on disease-free survival (DFS) and added toxicity

Triple-negative disease (CALGB 40603 and GermanGeparSixto trial)

- Significantly higher pCR rates with the addition of carboplatin to anthracycline- and taxane-based neoadjuvant chemotherapy (NACT) in TNBC
- In CALGB 40603 Trial:

  Addition of carboplatin to weekly paclitaxel followed by dose-dense doxorubicin-cyclophosphamide (AC): No improved EFS at three years, with improvement in pCR from 41 to 54%
- In GeparSixto Trial:

  Similar improvement of pCR to that observed in CALGB 40603

  Addition of weekly carboplatin: 10% absolute improvement in EFS

Triple-negative disease (CALGB 40603 and GeparSixto Trial)

- Carboplatin did not improve the frequency of lumpectomy
- Addition of carboplatin increased hematologic toxicities and dose modification
- Created uncertainties about the impact of carboplatin on outcomes in stage II to III TNBC
- No national guidelines recommend adding carboplatin to standard chemotherapy regimens

Cancer and Leukemia Group B (CALGB) 40603

- Patients (N = 443) with stage II to III TNBC
- Paclitaxel 80 mg/m(2) once per week for 12 weeks, followed by doxorubicin plus cyclophosphamide once every 2 weeks for four cycles
- Randomly assigned to concurrent carboplatin (AUC6) once every 3 weeks for four cycles and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles
- Effects of adding these agents on pCR breast (ypT0/is), pCR breast/axilla (ypT0/isN0), treatment delivery, and toxicities were analyzed

Cancer and Leukemia Group B (CALGB) 40603

- RESULTS: Either carboplatin or bevacizumab were less likely to complete wP and ddAC without skipped doses, dose modification, or early discontinuation resulting from toxicity
- Grade≥3 neutropenia and thrombocytopenia: more common with carboplatin, as were hypertension, infection, thromboembolic events, bleeding, and postoperative complications with bevacizumab
- Addition of either carboplatin (60% v 44%; P = .0018) or bevacizumab (59% v 48%; P = .0089) significantly increased pCR breast, whereas only carboplatin (54% v 41%; P = .0029) significantly raised pCR breast/axilla

Cancer and Leukemia Group B (CALGB) 40603

CONCLUSION:

- In stage II to III TNBC, addition of either carboplatin or bevacizumab to NACT increased pCR rates
- Improve relapse-free or overall survival? **unknown**
- The role of carboplatin could be evaluated in definitive studies

Neoadjuvant Endocrine Therapy

- Premenopausal:

  Limited to phase II studies

  Worse disease outcomes relative to chemotherapy

- Postmenopausal: (meta-analysis of 20 randomized trials with 3490 patients)

  Neoadjuvant endocrine therapy: Similar response rates and rates of breast-conserving surgery (BCS) with lower toxicity

  Survival data with neoadjuvant endocrine therapy not yet available

Choice of Endocrine Therapy

- Postmenopausal women: AI's instead of Tamoxifen

In the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial

- 377 postmenopausal women with stage II or III strongly ER-positive breast cancer
- Exemestane, Letrozole or Anastrozole for 16 to 18 weeks before surgery
- Similar response rates: 63% with exemestane, 75% with letrozole, and 69% with anastrozole
- No differences in the rate of BCS

Duration of Endocrine Therapy

- Four to six months
- If the tumor amenable to BCS after four to six months of endocrine therapy, proceed with definitive surgery
- If the tumor either stable or responding to therapy, but not yet amenable to BCS, discuss the risks and benefits of extending treatment to duration of 6 to 12 months versus proceeding with mastectomy

Post-NACT Evaluation and Treatment

Clinical assessment and indications for imaging

- Physical exam: Sufficient in most cases for assessment of tumor response
- Imaging: if helpful to guide the surgical approach
- Ultrasound (US): Breast and, if clinically positive prior to NACT, the ipsilateral axilla
- MRI: If not well visualized on US

Post-NACT Evaluation and Management of axilla

Clinically negative axilla prior to treatment (no pretreatment SLNB) — No evidence of lymph node involvement or negative needle biopsies of any suspicious nodes

Undergo post-NACT SLNB

- If SLNB negative (ypN0), no further axillary evaluation required. Treat with axillary radiation
- If SLNB positive (ypN+), proceed with ALND for those who have involvement of three or more sentinel nodes or involvement of a non-sentinel node
- One to two positive sentinel nodes: Favor axillary radiation
- Some experts prefer a completion ALND regardless of the number of sentinel lymph nodes involved after NACT

Positive axilla prior to treatment

- Clinical evidence of advanced nodal involvement (cN2 or cN3) prior to treatment: ALND should be pursued
- Clinical N1 disease or N0 disease with a positive axillary FNA or CNB prior to treatment, management depends on the response to NACT:

Patients who remain clinically node positive (ycN1) after NACT should undergo an ALND

Patients who are clinically node negative after NACT (ycN0) should undergo axillary ultrasound after NACT

Poor response or progression on neoadjuvant therapy

- Less than 5%: Tumor progression during NACT
- Stop therapy, instead of switching regimen, and proceed with surgery
- Mastectomy and, for those who continue to have involved lymph nodes, axillary dissection

Adjuvant treatment after surgery and NACT

- The indications for postoperative XRT: Depend on the **pretreatment stage** and **type of surgery**
- Hormone receptor-positive disease: Adjuvant endocrine therapy
- HER2-negative with residual invasive disease in the breast or lymph nodes, the administration of additional chemotherapy ? (Xoleda)
- HER2-positive disease:

  No demonstrated benefit of adjuvant chemotherapy

  Trastuzumab for full year

  The potential benefit of pertuzumab inadjuvant setting? **Unknown**

Adjuvant treatment after surgery and NACT

- Worse prognosis **without pCR**, especially with triple-negative or HER2-positive patients
- Routine use of further chemotherapy not recommended

The Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial:

- 900 patients with HER2-negative breast cancer (one-third: triple-negative disease) and residual disease after neoadjuvant anthracycline and/or taxane
- Eight cycles of capecitabine or no further chemotherapy
- Higher rates of five-year disease-free (74 versus 68%) and overall survival (89 versus 84%)
- Subgroup analyses: Improvement in disease-free survival in triple-negative patients (70 versus 56%)
- Toxicities: Diarrhea, neutropenia, and hand-foot syndrome