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Does Neoadjuvant Therapy Improve Disease Free Survival?

Cancer researchers and physicians have requested more detailed population-based treatment information regarding neoadjuvant therapy be collected in order to effectively respond to this question. They need to know whether neoadjuvant therapy was planned, then given as initially prescribed and how the tumor responded to it.

To improve everyone's understanding of the impact of neoadjuvant treatment. SEER added the following three new **Neoadjuvant Therapy data** items for collection for Dx Year 2021 and later:

- Neoadjuvant Therapy (NAACCR Item# 1632)
- Neoadjuvant Therapy–Clinical Response (NAACCR Item# 1633)
- Neoadjuvant Therapy – Treatment Effect (NAACCR Item# 1634)

We will use these new data items to collect information on whether neoadjuvant therapy was performed as well as the quality of care and outcomes for patients who received neoadjuvant therapy.

Before getting a basic overview of the new data items, let's go over some definitions as they relate to these data items:

- **Neoadjuvant therapy:** Systemic treatment (chemotherapy, endocrine/hormonal therapy, or biological/immunotherapy) and/or radiation therapy given prior to intended or performed surgical resection of the primary site. AKA: pre-surgical or preoperative treatment.

- **Limited systemic therapy:** Systemic treatment given prior to surgery, that is NOT a full course of neoadjuvant therapy intended to impact the extent of surgical resection or other outcomes. Limited systemic therapy may be given as part of a clinical trial to study the biology of a cancer or can be given in other circumstances (e.g., bridge therapy, pending surgery).

- **Surgical resection:** The most definitive surgical procedure to the primary tumor/site. Most often, this is surgery in the 30-80 code range with some exceptions based on primary site (e.g., Breast surgery codes in the 20's range are definitive surgical resections).

Now that we have some basic definitions, let's take a look at each data item.

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Neoadjuvant Therapy - Records whether the patient had neoadjuvant therapy prior to planned definitive surgical resection of the primary site. The codes and definitions are as follows:

Code	Description
0	No neoadjuvant therapy, no treatment before surgery, surgical resection not part of first course of treatment plan Autopsy only
1	Neoadjuvant therapy completed according to treatment plan and guidelines
2	Neoadjuvant therapy started, but not completed OR unknown if completed
3	Limited systemic exposure when the intent was not neoadjuvant; treatment did not meet the definition of neoadjuvant therapy
9	Unknown if neoadjuvant therapy performed

While the fact of neoadjuvant therapy can sometimes be inferred from the Surgery/Radiation Sequence and Surgery/Systemic Sequence data items, the coding instructions and resulting codes don't always clearly identify neoadjuvant therapy. The reason for this is that systemic and radiation treatment sequence with surgery data items really only captures the order in which codeable surgical procedures (Primary Site, Lymph Node or Other Reg/Dist Surgery) were performed in relation to radiation or systemic treatment; thus, they can't always be relied upon to identify cases with neoadjuvant treatment.

Example: Code 7 [Surgery both before and after systemic therapy] in the **Systemic Treatment/Surgery Sequence** field is problematic for breast cases, a site commonly treated with neoadjuvant therapy. In reviewing only the current SEER-required available treatment-associated codes, historically, it was not possible to distinguish between work-up and/or treatment protocols for breast cases that involve a lymph node biopsy, subsequent systemic treatment followed by primary site surgery vs. those initially treated with primary site surgery and subsequently treated with systemic treatment followed by further surgery to the primary site. However, the coding instructions for Systemic/Surgery Sequence have been updated for Dx Year 2021+ and a lymph node biopsy/FNA will no longer be included in this sequencing.

This change, along with the new Neoadjuvant Therapy data item will make it easier to identify true cases of neoadjuvant treatment.

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Neoadjuvant Therapy-Clinical Response - Records the clinical outcomes of neoadjuvant therapy as determined by the managing physician. The codes and definitions are as follows:

Code	Description
0	Neoadjuvant therapy not given
1	Complete clinical response (CR) *
2	Partial clinical response (PR) *
3	Progressive disease (PD) *
4	Stable disease (SD) *
5	No response (NR) * Not stated as progressive disease (PD) or stable disease (SD)
6	Neoadjuvant therapy done, managing/treating physician interpretation not available, treatment response inferred from imaging, biomarkers or yc stage
7	Complete clinical response based on biopsy results from a pathology report (per pathologist assessment)
8	Neoadjuvant therapy done, response not documented or unknown
9	Unknown if neoadjuvant therapy performed

*All of the clinical response codes 1-5, MUST come from a managing or treating physician statement, which will be based on clinical history, PE, biopsies, imaging studies and other diagnostic workup. If there is no physician statement of tumor response after neoadjuvant treatment, then only codes 6, 7, and 8 can be used. You cannot use information from the surgical resection pathology report to code this Clinical Response data item.

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Neoadjuvant Therapy-Treatment Effect - Records the **pathologist's statement** of neoadjuvant therapy treatment effect on the primary tumor/site, from the surgical pathology report.

This data item has Site-Specific schemas that should closely follow the CAP Cancer Protocol definitions. The Site-Specific schemas can be found online in the 2021 SEER Coding and Staging Manual, Appendix C: Site Specific Coding Modules, https://seer.cancer.gov/manuals/2021/appendixc.html.

The Site-Specific schemas are:

- Colon and Rectum, Esophagus, Stomach, Anus, Pancreas
- Lung
- Bone Appendicular, Pelvis, Spine
- Breast
- Ovary, Fallopian Tube, Primary Peritoneal
- Prostate
- All Other Schemas
- Thymus, Heart and Mediastinum, Retroperitoneum, Soft Tissue Abdomen and Thoracic, Soft Tissue Head and Neck, Soft Tissue Other, Soft Tissue Trunk and Extremities, GIST

The general coding structure for this data item is as follows:

Code	Description
0	Neoadjuvant therapy not given/no known presurgical therapy
1-4	Site-specific code; type of response
6	Neoadjuvant therapy completed and surgical resection performed, response not documented or unknown
7	Neoadjuvant therapy completed and planned surgical resection not performed
9	Unknown if neoadjuvant therapy performed Unknown if planned surgical procedure performed after completion of neoadjuvant therapy

In order to collect the information for these data items accurately, it will be important to document the physician's treatment plan along with information on whether the neoadjuvant treatment was completed according to the plan (i.e., number of cycles completed). A physician statement of the patient completing neoadjuvant therapy is sufficient to indicate the patient completed neoadjuvant treatment according to the recommended treatment guidelines. In addition, the post-systemic/radiation treatment clinical evaluation information, which we generally aren't accustomed to documenting, will need to be abstracted to support the coding of the Neoadjuvant Therapy – Clinical Response data item.

Information on recommended neoadjuvant treatment guidelines by primary site can be found in the NCCN guidelines, ASCO guidelines or other available treatment guidelines.

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Conclusion:

These neoadjuvant treatment data items will provide valuable quality of care and outcomes information that SEER has not collected before. With this data collection effort we will improve our understanding of the impact of neoadjuvant therapy on patients with locally advanced disease. SEER will be better able to assess whether this treatment effectively decreases the tumor burden and enables surgeons to perform curative resections that ultimately reduce the risk of recurrence. Quantifying the extent of therapy-induced tumor regression is important because it will provide a better risk stratification for those patients who receive neoadjuvant therapy and contribute to the assessment of cancer care quality.

Case Scenario:

2/1/2021 Rt breast core biopsy: Invasive ductal carcinoma, Nottingham score: 9. ER: negative; PR: negative; HER2 IHC: negative (1+)

2/28/2021 Oncology consult: Pt w/T2 N0 triple negative invasive breast cancer. Plan: Neoadjuvant therapy with washout period prior to surgery.

3/5/2021 Adriamycin, Cytoxan and Taxol started.

7/1/2021 Breast MRI: Rt breast interval response to neoadjuvant therapy with no residual enhancement at the site of biopsy-proven malignancy at 10:00. BI-RADS category 6.

7/15/2021 Oncology note – IMP/Plan: Pt is s/p neoadjuvant treatment, on PE there was no residual palpable mass. MRI was reviewed, which showed resolution. Based on all this, pt appears to have had an excellent clinical response to her neoadjuvant therapy. Proceed with surgery in 2-6 weeks.

8/15/2021 Bilateral nipple sparing mastectomy with SLNB – pathology report:

FINAL DX
SUMMARY CANCER DATA - Breast, Invasive
Specimen and procedure
Procedure: Total mastectomy (including nipple-sparing and skin-sparing mastectomy)
Specimen laterality: Right
Primary tumor (status post pre-surgical therapy): No evidence of residual invasive carcinoma
Estimated treatment response in breast: Complete pathologic response (no residual invasive carcinoma)

Pre-treatment tumor characteristics:
- Pre-treatment Nottingham grade: Grade III: 8-9 points
- Pre-treatment ER: Negative
- Pre-treatment PR: Negative
- Pre-treatment her 2 by IHC: Negative for her 2 overexpression by IHC

Additional findings:
- DCIS (ductal carcinoma in situ): DCIS not identified
- Changes consistent with previous biopsy site: Present

Margins:
- Final surgical resection margins (including separately submitted margins): Invasive carcinoma margins: Not applicable (no invasive carcinoma present)
- DCIS margin: Not applicable (no DCIS present)

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Lymph node involvement (S/P neoadjuvant therapy):

- Sentinel lymph nodes: Sentinel nodes with carcinoma 0 / Total sentinel nodes 4
- Non-sentinel nodes: Non-sentinel nodes with carcinoma 0 / Total non-sentinel nodes 0
  - ✓ Total number of nodes with macrometastases: 0
  - ✓ Total number of nodes with micrometastases: 0
  - ✓ Total number of nodes with isolated tumor cells: 0
- Evidence of nodal treatment response: No definite treatment response

PATHOLOGIC STAGE CLASSIFICATION (pTNM, AJCC 8th Edition)

- Primary Tumor (pT): ypT0: No evidence of residual invasive or in situ tumor
- Regional nodes (pN): ypN0: No regional lymph node metastasis histologically (ITCs may be present)
- N stage modifier: Not applicable

Neoadjuvant Treatment Data Item Coding:

Neoadjuvant Therapy: Code 1 – Neoadjuvant therapy completed according to treatment plan and guidelines.

Rationale: The 7/15/2021 Oncology note states the patient completed neoadjuvant treatment.

Neoadjuvant Therapy–Clinical Response: Code 1 – Complete clinical response (CR).
Rationale: The 7/15/2021 oncology assessment after neoadjuvant treatment states there was no residual palpable mass; the MRI showed tumor resolution and there was a statement of an excellent clinical response. While "complete clinical response" wasn't specifically stated, combining the MD statement, PE, and imaging findings, this is indicative of a complete clinical response.

Neoadjuvant Therapy–Treatment Effect: Breast Schema Code 1 – No residual invasive carcinoma present in the breast after presurgical therapy.

Rationale: The pathology report from the post neoadjuvant bilateral nipple sparing mastectomies states "Complete pathologic response (no residual invasive carcinoma)."

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