Current and Future Cancer Staging After Neoadjuvant Treatment for Solid Tumors

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Abstract: Until recently, cancer registries have only collected cancer clinical stage at diagnosis, before any therapy, and pathological stage after surgical resection, provided no treatment has been given before the surgery, but they have not collected stage data after neoadjuvant therapy (NAT). Because NAT is increasingly being used to treat a variety of tumors, it has become important to make the distinction between both the clinical and the pathological assessment without NAT and the assessment after NAT to avoid any misunderstanding of the significance of the clinical and pathological findings. It also is important that cancer registries collect data after NAT to assess response and effectiveness of this treatment approach on a population basis. The prefix y is used to denote stage after NAT. Currently, cancer registries of the American College of Surgeons’ Commission on Cancer only partially collect y stage data, and data on the clinical response to NAT (yc or posttherapy clinical information) are not collected or recorded in a standardized fashion. In addition to NAT, nonoperative management after radiation and chemotherapy is being used with increasing frequency in rectal cancer and may be expanded to other treatment sites. Using examples from breast, rectal, and esophageal cancers, the pathological and imaging changes seen after NAT are reviewed to demonstrate appropriate staging.

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Introduction

Neoadjuvant (nonsurgical) initial treatment of nonmetastatic solid tumors is rapidly increasing and has become the standard of care for patients with many different cancers. However, the collection of data on treatment response, subsequent surgery, prognosis, and survival has lagged behind this trend. In this review, we explain why this happened, why it is essential to collect these data, and how we can bridge this data gap.

Until the late 1960s, treatment with curative intent for solid tumors consisted almost exclusively of complete surgical removal of the primary tumor and regional draining lymph nodes (notable exceptions include some gynecological and head and neck cancers that could be cured with radiation therapy alone, dating back to the 1930s and 1940s). Unfortunately, the same cancer would often recur, presumably because of clinically unapparent distant metastases. Although cytotoxic and hormonal drugs were given to prolong lives in patients with metastatic cancer, studies using these drugs as adjuvants to enhance survival in patients after complete surgery did not begin until the 1960s and 1970s with the use of 5-fluorouracil in colorectal cancer and breast cancer and tamoxifen in estrogen receptor-positive breast cancer. As more effective drugs were developed, drug-related toxicities were reduced, and management of side effects improved, more patients were offered adjuvant chemotherapy for the treatment of presumed micrometastatic disease.

American Joint Committee on Cancer (AJCC) staging has been used to provide prognostic information for patients and providers, guide treatment recommendations, and establish longitudinal survival outcomes for the cancer surveillance...
community.\textsuperscript{1} Clinical staging (cTNM) uses data collected from the patient’s history and physical examination and imaging findings to classify (or describe) the extent of disease and provide prognostic and treatment recommendations. Pathological staging (pTNM) includes the clinical stage information modified by the operative findings and the pathological examination of the specimen resected at surgery.\textsuperscript{1,2} Well established collaborations have developed between surgeons, radiation oncologists, medical oncologists, pathologists, radiologists, and cancer registrars to collect and submit clinical and pathological TNM stage data to institutional databases and the National Cancer Database (NCDB).

Until the 1980s, nearly all patients without distant metastatic disease at diagnosis underwent surgery. A new approach to the multimodality treatment of cancer began in the 1980s, first in patients with locally advanced cancers for which combination therapy was indicated. Instead of starting with surgery, primary chemotherapy frequently was given to determine in vivo chemosensitivity and reduce the burden of local and regional disease. The rationale for neoadjuvant therapy (NAT) is listed below.

The Clinical Case for Giving NAT

1. The life-threatening aspect of solid tumors is nearly always distant metastatic disease and is rarely local or regional disease.
2. Neoadjuvant systemic therapies treat occult distant metastatic disease at the earliest point in time.
3. Primary tumor sensitivity to these therapies can be assessed by measuring and documenting tumor response.
4. Development or progression of distant metastatic disease can be assessed, and an alternative systemic treatment may be indicated before surgical resection if it is still considered appropriate.
5. A response to NAT may reduce local tumor burden to allow less extensive surgery (or sometimes nonsurgical management) and may increase the likelihood of complete resection with negative pathological surgical margins, thereby reducing the risk of local or regional recurrence.

This neoadjuvant approach before surgical excision is distinct from situations in which chemoradiation is given as definitive treatment, such as anal cancer and some head and neck cancers. With this neoadjuvant approach, staging of these patients began with clinical staging. However, after initial treatment, there was a second clinical staging time point before surgery, designated ycTNM, where the prefix y was used to denote preoperative treatment,\textsuperscript{3,4} and c similarly was used to denote findings from the history and physical examination and imaging before surgery. In addition, nearly all of these patients went on to have definitive surgery, which included operative findings and resected specimens and resulted in ypTNM staging designation (Fig. 1). To make the important distinction between an assessment without NAT and a clinical and pathological assessment after NAT and to avoid any misunderstanding of the significance of the

![AJCC Stage Classifications](image-url)

**FIGURE 1.** Clinical Staging Occurs After Diagnosis and Staging Workup and Is Recorded in the Medical Record as cTNM. If the first treatment is surgical resection, pathological staging occurs with the pathological findings and is recorded as pTNM. If the first treatment is systemic treatment, posttreatment evaluation by examination and imaging and postneoadjuvant clinical stage may be recorded as ycTNM. If surgical resection is performed, then postneoadjuvant pathological staging occurs with the pathological findings and is recorded as ypTNM.
findings, the y prefix was first introduced in the third edition of the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours in 1978 and in the third edition of the AJCC Cancer Staging Manual in 1988. Despite the introduction of the y prefix, cancer registries not accredited by the American College of Surgeons’ Commission on Cancer (CoC) were not required to collect yp data until the introduction of the Collaborative Stage Data Collection System in 2004.

**Definitions of Neoadjuvant Treatment**

Systemic NAT may include infusional or oral chemotherapy, hormonal therapy, targeted agent oral therapy, or infusional immunotherapy. NAT may also include radiation therapy, either alone or in combination with systemic therapies. The duration of NAT is defined as a therapeutic course of treatment before surgery is performed. A therapeutic course that is interrupted by excessive toxicity, other intolerance to treatment, or clinical progression of disease is not considered or included as NAT for staging purposes. Also, a short (days or weeks) course of chemotherapy or hormonal therapy looking for early markers of response is not considered or included as NAT for staging purposes.

**Defining the Pathological Response to Primary Tumors and Nodal Metastases After NAT (yp)**

The assessment of pathologic response to NAT includes the usual staging parameters assessed after definitive surgical resection, such as residual tumor size, depth of invasion, and nodal status, but may also include other factors that do not influence stage. These include margin status, the presence of lymphovascular invasion, residual tumor volume/tumor burden, and various scoring systems for partial response (PR) and complete response (CR). Appropriate pathological assessment in the setting of NAT can be challenging for pathologists who do not focus their practice on neoplastic surgical pathology. This includes gross specimen assessment, understanding pathological changes associated with NAT, assessment of tumor burden, as well as understanding and applying the rules for staging with NAT.

**Primary tumor**

The residual tumor size may not reflect the extent of viable tumor. The span of the original tumor may be replaced by nonneoplastic stroma, fibrosis, necrosis, and inflammatory and immune cell infiltrates, with or without residual viable malignant cells. There have been many attempts to characterize and quantify this tumor response, most often with broad categories such as pathological CR (pCR), PR (pPR), or no response (pNR). Several detailed scoring systems have been proposed, and some have been widely accepted, to describe the response to treatment in breast, lung, rectal, esophageal, and pancreatic carcinomas as well as osteosarcoma and Ewing sarcoma. Multiple studies have shown improved survival when a pCR is seen after NAT in colorectal, breast, pancreatic, and esophageal carcinomas. However, in the eighth edition of the AJCC Cancer Staging Manual, there were sufficient data to build and validate prognostic ypTNM tables only for esophageal and gastric carcinoma. Similar yTNM tables are under construction in a forthcoming AJCC version 9 update in breast cancer staging.

**Lymph nodes**

Pathological evaluation of treatment response in regional lymph nodes involved with tumor after NAT includes histopathological and sometimes immunohistochemical staining. Nodes involved by tumor have responses similar to those seen in the primary: pCR, pPR, or pNR. When all nodes are negative by histopathological examination, the N category becomes ypN0. For nodes that have residual tumor, the number and location of positive lymph nodes are recorded, and the N category becomes ypN1-ypN3. The presence of individual tumor cells (defined as small clusters of tumor cells <0.2 mm in dimension) is considered negative (ypN0[i+]) for most solid tumors, except in patients with melanoma, in whom the presence of any tumor cell(s) is considered to portend a prognosis worse than negative nodes and should be designated as a tumor-positive lymph node (ypN1-ypN3). The size of the largest metastatic deposit and the presence or absence of extranodal extension are recorded. These are not included in ypTMN but may affect treatment recommendations. Treated nodes may show fibrosis, necrosis, and an inflammatory or immune cell infiltrate, suggesting a nodal metastasis with a pCR, even if pretreatment biopsy was not performed. The presence of this treatment effect may be recorded in synoptic pathology reports but currently is not collected by cancer registrars, and the prognostic significance is unknown. This does not change the clinical stage. If no sentinel node biopsy or lymphadenectomy is performed after NAT, the ypNX classification is used.

**Defining the Response to NAT by Imaging (yc or Posttherapy Clinical)**

The concept of yp is well known by most clinicians who use NAT. Less well known but also important to record is the use of yc to document the clinical response to NAT. In addition to physical examination, anatomical and functional imaging is central to clinical cancer staging for defining the local extent of tumor and the presence of regional or distant metastases before the start of treatment (cTMN) and after NAT (ycTMN). Whenever possible, confirmation, at least by needle biopsy, is indicated.

**Primary tumor**

Imaging of the primary tumor may include the size, number (unifocal, multifocal, multicentric, satellite lesions) and
location as well as local invasion or penetration into surrounding structures. Surface or endoscopic ultrasound (EUS) and cross-sectional anatomical imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) are most frequently used to clinically stage a patient before treatment (cT). Functional imaging, such as diffusion-weighted imaging (DWI) sequence MRI, as described below for rectal cancer, can also aid in assessment of the primary. In general, after NAT, the same imaging modality that was used before treatment is preferred to best compare and estimate the clinical response, resulting in ycT designation.

**Lymph nodes**
In addition to ultrasound and cross-sectional anatomical imaging, functional imaging by fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) scanning frequently is added to clinically stage primary tumors that are locally advanced at diagnosis or are prone to earlier nodal or distant metastases. Abnormal lymph nodes, by size criteria or other characteristics such as shape, blood flow, or loss of a fatty hilum, should undergo core-needle or fine-needle biopsy to confirm metastatic cells, because there is a fairly high false-positive rate by relying on physical examination or imaging alone to describe nodal metastasis. After needle biopsy confirmation of metastasis in an abnormal node, but without lymph nodes having been removed, the designation is still clinical (cN1). After NAT, if nodes remain abnormal on imaging, they remain clinically positive and are designated ycN1. If these nodes appear normal on imaging after NAT, the designation becomes ycN0. Currently, most patients then undergo surgical resection by completion lymphadenectomy, and the designation becomes ypN1-ypN3 or ypN0. If only a sentinel lymph node biopsy (SLNB) is performed after NAT, the designation is ypN0(sn) if there is a pCR or ypN1-ypN3(sn) if the sentinel node(s) are microscopically positive. If a completion lymphadenectomy then is performed for a positive sentinel node, the final designation will include the total number of positive nodes (sentinel and nonsentinel nodes) as ypN1-ypN3, and the (sn) designation is omitted.

**Distant metastasis**
The M designation after NAT is more straightforward. If a distant lesion on imaging is highly suggestive of a metastasis, the clinical designation is cM1. If no biopsy is performed before NAT, the designation remains cM1. At least one site of any abnormal imaging findings that suggest a distant metastasis after diagnosis should undergo biopsy if it can be performed safely. If a distant site is positive by needle biopsy, the designation is pM1 and remains pM1 throughout the course of treatment, even if the metastasis resolves and is not present on imaging after treatment. Even if the patient’s stage is cM0 before NAT, it is important that imaging done after NAT includes an assessment for distant metastases, as metastases can develop during the course of NAT if the tumor is resistant to any systemic therapy. Designations of pM0, pMX, or cMX are not valid categories and should not be assigned. There is considerable interest in using imaging to determine a pCR after NAT.

To determine the response to treatment after NAT, it is essential to record the pretreatment clinical stage and compare this with the posttreatment clinical stage as well as the posttreatment pathological stage. The eighth edition of the *AJCC Cancer Staging Manual* uses the combination of T, N, and M categories and prognostic factors to define stage group tables for prognosis and as a guide for further treatment. Currently, there are major gaps and limitations in data collection and data definitions, as illustrated by the case examples below.

**Case I: Breast**
A woman aged 45 years with a strong family history of breast cancer undergoes screening MRI and is found to have a 2.2-cm spiculated mass in the upper outer quadrant of the left breast. By palpation, there is one abnormal left axillary node. Figure 2A demonstrates the primary tumor
and lymph node as seen on the MRI. Core-needle biopsies of the breast mass and abnormal axillary node reveal invasive ductal carcinoma, grade 3, that is ER-negative, PR-negative, and has no amplification of HER-2 (triple-negative), as well as metastatic carcinoma in the axillary node. The clinical prognostic stage is cT2 cN1 cM0; grade 3; HER2-negative, ER-negative, PR-negative; stage group IIIB. FDG-PET/CT imaging reveals no evidence of distant metastatic disease. She receives neoadjuvant chemotherapy (NACT). After 4 months of treatment, her primary tumor and abnormal axillary node are no longer palpable and are not seen on the MRI, as illustrated in Figure 2B. MRI of the breast is the most sensitive and specific imaging test to determine response after completion of NACT, but it is most useful if there is a pretreatment MRI for comparison. If it is clinically desirable to assess residual axillary lymphadenopathy by imaging after completion of NACT, axillary ultrasound remains the best imaging examination. If there is clinical concern about distant metastases, FDG-PET/CT is the best imaging procedure. There is considerable interest in using imaging to determine whether there is a pCR after NAT. However, in trials to date, posttreatment imaging showing complete clinical response in the breast and axilla (cCR) have not been accurate enough to eliminate the need for surgery to assure the removal of subclinical residual disease.

Her y-clinical stage is now ycT0 ycN0 cM0. Currently, there are no data fields for yc designation in cancer registry software; therefore, no ycTNM categories or stage group is entered. The patient undergoes a partial mastectomy and SLNB. Pathology reveals no residual invasive carcinoma in the breast, and 3 sentinel nodes are negative for tumor. No further lymphadenectomy is performed. Her yp-pathological stage is ypT0 ypN0(sn) cM0. The data used by the expert panel members for developing the eighth edition of the AJCC Cancer Staging Manual did not include a survival analysis for patients who receive NACT. Therefore, there is no final stage group entered for this patient.

The take-home messages and implications from case I are: 1) subsets of primary breast cancer, such as a triple-negative phenotype, respond very well to NACT; 2) complete clinical and pathological responses are increasingly common; 3) completion lymph node dissection is performed less often when SLNB results are negative; 4) although ypTNM data are collected, no stage group table is available; and 5) clinicians have the information needed to care for the patient, but the implications for prognosis and survival are just beginning to be understood.

Case II: Rectum
A woman aged 56 years seeks medical attention because of rectal bleeding. A rectal examination reveals a mass 5 cm from the anal verge. This is confirmed on endoscopy (Fig. 3A), and biopsy reveals moderately differentiated adenocarcinoma. A pelvic MRI shows a 5-cm-long tumor that extends into the mesorectum (Fig. 3B) and mesorectal lymph nodes, but none are enlarged or have an irregular border, and they are considered normal. A CT scan of the chest, abdomen, and pelvis shows no evidence of metastatic disease (clinical metastasis status, cM0). The tumor is staged as cT3 cN0 cM0, stage group II A. She receives chemoradiation. Six weeks after completion, a pelvic MRI shows that the tumor is smaller but still extends into the mesorectum.

The recommended MRI protocol for restaging is similar to that for primary staging. However, recent consensus guidelines recommend routinely including a DWI
sequence in the restaging protocol.\textsuperscript{25} High signal on DWI at the location of the tumor bed indicates residual tumor, whereas the absence of signal is suggestive of a CR. Suggested timing for postneoadjuvant therapy MRI is about 8 weeks after completion of NAT.\textsuperscript{26} As a result of successful response to treatment, rectal tumors typically decrease in size on MRI while undergoing a fibrotic transformation. Untreated (nonmucinous) tumors show intermediate signal intensity on T2-weighted MRI. When tumor tissue becomes fibrotic, the signal drops considerably, and the tumor bed becomes markedly hypointense. A small minority of tumors develop a mucinous response as a result of NAT (as in this example), leading to an increase in signal. Therefore, based on the signal changes, a 5-point MRI tumor regression grade (mrTRG) classification has been developed, which is similar to the TRG system commonly used in histopathology. Unfortunately, agreement between the mrTRG and pathological TRG in performance to identify complete responders is rather low. Nevertheless, although MRI has known difficulties in differentiating between fibrosis and vital tumor cells, MRI is often helpful to surgeons for determining their operative strategy after NAT (see case IV, below).\textsuperscript{25,27,28}

The posttherapy clinical stage is now ycT3 ycN0 cM0. Surgery is performed the following week. The pathology report states that, although there are pools of acellular mucin, there are no residual malignant cells identified, and the tumor regression score is zero (modified Ryan scheme).\textsuperscript{1,8} No tumor is identified in 2 lymph nodes. The posttherapy pathological stage is ypT0 ypN0 cM0. There is no prognostic stage group assignment when there is a pCR. In rectal cancer, it is known that both the time interval to surgery and the dose of radiation can influence tumor response found at the time of surgery, but not necessarily actual patient survival, so, until now, the AJCC colorectal expert panel has not developed yTNM stage tables.

The take-home messages and implications from case II are: 1) clinical T category estimation of rectal carcinoma is primarily based on imaging; 2) ycTNM stage data are not currently collected by cancer registries; and 3) there is only one prognostic stage group table for colorectal carcinoma that includes TNM data at the end of all treatment. The stage table does not denote pTNM versus ypTNM; however, these data are collected by cancer registrars as ypTNM, and the stage table is used to assign the yp stage group along with the tumor regression score. For the future, the data will need to be analyzed to determine whether separate stage group tables are necessary for c, p, or yp.

**Case III: Esophagus**

A woman aged 53 years with a 3-month history of difficulty in swallowing undergoes an esophagoscopy, which shows abnormal nodularity 25 to 35 cm from the incisors. Biopsy of this area reveals squamous cell carcinoma, and she undergoes EUS, CT of the thorax and abdomen, and FDG-PET scans. The CT scans show thickening of the esophagus but no evidence of metastases in the chest or abdomen. The EUS shows invasion of the muscularis propria (cT2). The FDG-PET scan shows uptake in the midesophagus (Fig. 4A), FDG-PET avidity in 2 left gastric lymph nodes (Fig. 4B), and no evidence of metastases.

The cTNM stage is cT2 cN1 cM0, clinical stage II. She undergoes preoperative chemoradiation. Restaging by imaging shows persistent midesophageal uptake on FDG-PET but no abnormal nodes. EUS suggests invasion of the

![FIGURE 4. A Woman Aged 53 Years Presents With Dysphagia. A computed tomography scan revealed mild thickening of the esophagus. Endoscopic ultrasound reveals a carcinoma with infiltration of the muscularis propria (clinical tumor classification, cT2). (A) A fluorodeoxyglucose-positron emission tomography image shows midesophageal uptake, and (B) there is also uptake in 2 left gastric lymph nodes (clinical lymph node status, cN2).](image-url)
submucosa only. FDG-PET/CT scans and EUS are the imaging modalities recommended for initial staging and also for restaging after NAT. Nevertheless, it is recognized that neither the sensitivity nor the specificity of restaging by FDG-PET/CT and/or EUS is high enough to spare patients unnecessary (or futile) operations. However, emerging data from trials using MRI suggest that morphologic and diffusion-weighted MR scans may be superior to both FDG-PET/CT and EUS in the posttherapy setting and may have an important role in determining nonoperative management (NOM).

Her ycTNM stage is ycT1 ycN0 cM0. There is no yc stage group for cancers of the esophagus. Surgical pathology from the esophageal resection shows residual tumor in the lamina propria (ypT1a) with a regression score of 2 (modified Ryan scheme) but no tumor involvement of any of the 30 identified lymph nodes (ypN0). There is yp stage grouping in esophageal cancer. The yp stage group is yp stage I.

Esophageal cancer, unlike both breast and rectal cancer, has stage tables for cTNM, pTNM, and ypTNM (but not ycTNM). In breast and rectal cancer, TNM can be used to describe and record the response to treatment and also can be used to help direct subsequent therapies, but it is not as useful to help indicate prognosis. The yp stage table in esophageal cancer was possible because of the robust database collected by the Worldwide Esophageal Cancer Collaboration.

The take-home messages and implications from case III are: 1) clinical T category estimation of esophageal carcinoma is primarily based on imaging; 2) ycTNM stage data are not currently collected by cancer registries; and 3) there are prognostic yp, but not yc, stage group tables for esophageal carcinoma that include TNM data at the end of all treatment. When NOM of esophageal cancer begins, collection of yc data will be essential to determine the response to treatment.

Nonoperative Management
In certain tumor sites, such as squamous cell carcinoma of the anal canal and larynx, chemoradiation has been used for curative treatment, with the advantage of anal sphincter preservation and voice preservation. There is increasing evidence that, in some sites such as adenocarcinoma of the rectum, if a CR to chemoradiation is achieved (ycCR), a patient can be carefully followed clinically and, unless there is recurrence, surgery may not be necessary. This NOM is being increasingly considered. The appropriateness of nonoperative cancer treatment may be difficult to assess by conventional phase 3 clinical trials, as patients are unlikely to accept randomization between a nonoperative approach and a permanent stoma. Confirmation of the value and safety of this approach will probably need population-based surveillance data, so it is vital that both clinical stage (cTNM) and yc stage (ycTNM), as well as initial treatment intent, are recorded to assess the effectiveness of NOM.

Case IV: Rectal Cancer NOM
The woman aged 56 years described in case II above undergoes chemoradiation and, at 6 weeks after completion, endoscopy shows no residual tumor (Fig. 5A), and a restaging MRI shows minimal fibrosis and no evidence of residual tumor (Fig. 5B). The standard recommendation would be surgery, but an abdominoperineal resection may be required. Active surveillance without surgery is currently under study in phase 2 clinical trials as an option in this situation and is likely to be increasingly considered as CRs to NAT become more common. The posttherapy clinical stage is ycT0 ycN0 cM0. These data elements need to be collected and recorded in CoC cancer registries to determine the effectiveness of such an approach.
The take-home messages and implications from case IV are: 1) clinical T category estimation of rectal carcinoma is primarily based on imaging (see imaging comments in case II, above); 2) ycTNM stage data are not currently collected by cancer registries; and 3) collection of ycTNM will be needed to validate recurrence rates and prognosis of NOM.

Discussion

In the eighth edition of the AJCC Cancer Staging Manual, for most solid tumors (including lung, pancreas, liver, colorectal, prostate, bone, soft tissue sarcoma, gynecological and genitourinary cancers, thyroid, and most head and neck carcinomas), there is a single prognostic stage group table with no separation of clinical and pathological stage groups. The implication in each of these chapters is that pathological staging will always be more accurate and will supplant clinical staging, and surgery will be performed for the majority of these tumors. Staging of breast carcinoma, melanoma, human papillomavirus-mediated (p16-positive) oropharyngeal carcinoma, and Merkel cell carcinoma includes separate clinical (cTNM) and pathological (pTNM) stage group tables. For esophageal and stomach carcinomas, there are separate clinical, pathological, and posttherapy pathological (yp) stage group tables.

The primary databases for updating AJCC cancer staging reside in the NCDB as well as several international collaborative databases, such as the International Association for the Study of Lung Cancer, the Worldwide Esophageal Cancer Collaboration, the International Gastric Cancer Association, the International Federation of Gynecology and Obstetrics, and others. The NCDB is a large clinical oncology database sourced from hospital registry data collected in more than 1500 facilities. The NCDB represents >70% of newly diagnosed cancer cases nationwide and includes more than 34 million historical records. As systemic treatments become more effective, showing an increased likelihood of partial or complete clinical responses for many disease sites, the application of NAT will increase. There is a need to expand the data collected through CoC-accredited cancer registries and the NCDB. National cancer registry data fields do not exist for yc collection, and definitions for therapeutic NAT are not well defined or standardized. Physicians can facilitate the documentation of neoadjuvant cases for cancer registries by clearly identifying the treatment intent in the clinical record. NAT data are not currently needed or used by the cancer surveillance community. It is essential for the clinical cancer care community to give voice to this need, or we risk not being able to have evidence for the impact and outcomes of patients undergoing NAT in general, especially when nonoperative treatment becomes more prevalent. In addition to the CoC-accredited cancer registries, the AJCC is partnering with the National Program of Cancer Registries of the Centers for Disease Control and Prevention, the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, and the national cancer registry associations (the North American Association of Central Cancer Registries and the National Cancer Registrars Association) to prioritize the future collection and reporting of yc and yp data in patients undergoing NAT to enable the collection of population-based data.

Although appropriate pathological assessment after NAT is largely well defined in such tumors as rectal and breast cancers, it is less so in other tumors. Because NAT is increasingly being used in other tumor sites, there is a need to standardize the approach to pathological assessment of the definitive resection specimen, including assessing for tumor burden and tumor response as well as the use of evidence-based scoring systems.

To further complicate the data gap challenge, in addition to traditional cytotoxic chemotherapy, NATs are rapidly expanding to include immunotherapy or oral targeted therapies, alone or in combination with chemotherapy and radiation therapy. There may also be a need in the future to collect response data other than TNM, such as circulating tumor cells, molecular responses, circulating cell-free tumor nucleic acids, and even humoral, cellular, and/or tissue immune responses, as they become ever more relevant. The effort to define harmonized data elements for these responses and the development of processes and standards to collect these elements into centralized cancer databases will require collaboration, commitment, and additional resources of funding from all stakeholders in the clinical cancer care and cancer research communities.

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