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EDITORIAL – COLORECTAL CANCER

Updates on the Version 9 American Joint Committee on Cancer Staging System for Anal Cancer

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Since its first edition was published in 1977, the American Joint Committee on Cancer (AJCC) has remained the authority on cancer staging for nearly all malignancies, including anal cancer.[1] Importantly, the AJCC staging system has created a common language for cancer risk stratification, allowing cancer care providers across the world to effectively communicate about tumor burden and treatment paradigms. Not only does the AJCC staging system provide prognostic information regarding the estimated survival for patients with cancer but it also plays a vital part in cancer research, including eligibility for practice-changing clinical trials. Additionally, AJCC cancer staging is a critical tool in cancer epidemiology and population health, as the structured framework and consistency allows for tracking of trends and comparison of data over time and across the globe. The AJCC staging system undergoes periodic revisions in order to ensure that the contemporary staging definitions reflect evolving practice patterns and survival outcomes for each primary disease site.

As the incidence of anal cancer has continued to increase over the past several years,[2] maintaining up-to-date stage groupings among this changing population is crucial. For most patients with anal cancer, upfront definitive chemoradiation is the standard of care and it is therefore critical that the clinical stage is correctly assigned as patients' prognosis varies widely based on the initial stage at presentation.[3] The most recent version of the AJCC staging system for anal cancer, version 9, was published in 2022 with a required use date of 1 January 2023, and included several critical updates to the overall stage group definitions.[4] Notably, these updated staging criteria were informed through the use of a newly developed, data-driven approach adopted by the AJCC, incorporating contemporary survival data to refine stage groupings so that they demonstrated hierarchical prognostic order.[5]

After evaluating survival outcomes using the National Cancer Database (NCDB) according to the AJCC 8th Edition staging system, the expert panel identified that stage IIIA disease, as previously defined, had better survival than stage IIB disease, thus necessitating revision.[5] Specifically, key changes within the AJCC Version 9 staging system for anal cancer include the following: (1) revising stage IIB from T3N0M0 to T1-T2N1M0 disease; (2) revising stage IIIA from T1-T2N1M0 to T3N0-N1M0 disease; (3) revising stage IIIC from T3-T4N1M0 to T4N1M0; and (4) eliminating stage 0 disease from the staging system for anal cancer entirely (Table 1). Based on these changes, the recently published AJCC Version 9 staging system for anal cancer, which applies to all carcinomas originating in the anal canal,[4] now ensures that each increase in stage portends a worse prognosis than the previous group (Fig. 1).

STAGE IIB DEFINED AS T1-T2N1M0

While the individual definitions of each T, N, and M category in the AJCC Version 9 staging system for anal cancer have remained largely consistent with prior 8th edition criteria (with the exception of obturator nodes now being included in the definition of N1a disease), notable modifications have been made to the TNM combinations that define the overall stage groupings. One specific change

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TABLE 1 American Joint Committee on Cancer Version 9 staging system for anal cancer stage-group definitions.

When T is …	And N is …	And M is …	Then the stage group is …
T1	N0	M0	I
T2	N0	M0	IIA
T1-T2	N1	M0	IIB
T3	N0-N1	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIC
Any T	Any N	M1	IV

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redefined stage IIB disease from T3N0M0 to T1-T2N1M0. Thus, evaluating overall survival data to refine stage groups not only highlighted the importance of assessing the interaction between each T, N, and M category combination that inform overall stage but underscores that larger tumor size portends a worse prognosis than positive nodal disease.

This finding may in part be attributable to substantial developments made over the past decade in increasing the accessibility and precision of imaging modalities necessary for the clinical staging of anal cancer. As described in a recent review on anal cancer staging, the relatively reduced association between prognosis and nodal status in comparison with tumor size suggests that smaller, yet clinically positive lymph nodes may have previously gone undetected due to older, less sensitive imaging modalities.[6] However, in an era with improved identification and imaging techniques, this likely represents an overreporting of clinical lymph node status, which may actually be of little clinical significance, previously leading to classification as a higher overall stage.

Both magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose–positron emission tomography combined with computed tomography (PET/CT) have been increasingly utilized for the clinical staging of anal cancer, and offer improved diagnostic capabilities when compared with standard CT alone.[7,8] Specifically, pelvic MRI was officially introduced into anal cancer clinical practice guidelines in 2010 after it was found to have increased accuracy in defining the clinical T category, based on tumor size, compared with standard CT,[9] while PET/CT has demonstrated increased specificity for locoregional lymph node involvement.[10,11] However, despite the frequent use of both pelvic MRI and PET/CT in the clinical staging of anal cancer, national guidelines are currently lacking to inform the use of one imaging modality over another. Thus, future research that uses high-quality data to further define the role of MRI and PET/CT in anal cancer staging is needed.

STAGE IIIA DEFINED AS T3N0-N1M0, AND STAGE IIIC DEFINED AS T4N1M0

Another noteworthy update to the AJCC Version 9 staging system for anal cancer worth highlighting is the change in stage IIIA disease, redefined from T1-T2N1M0 to T3N0-N1M0, and stage IIIC disease, redefined from

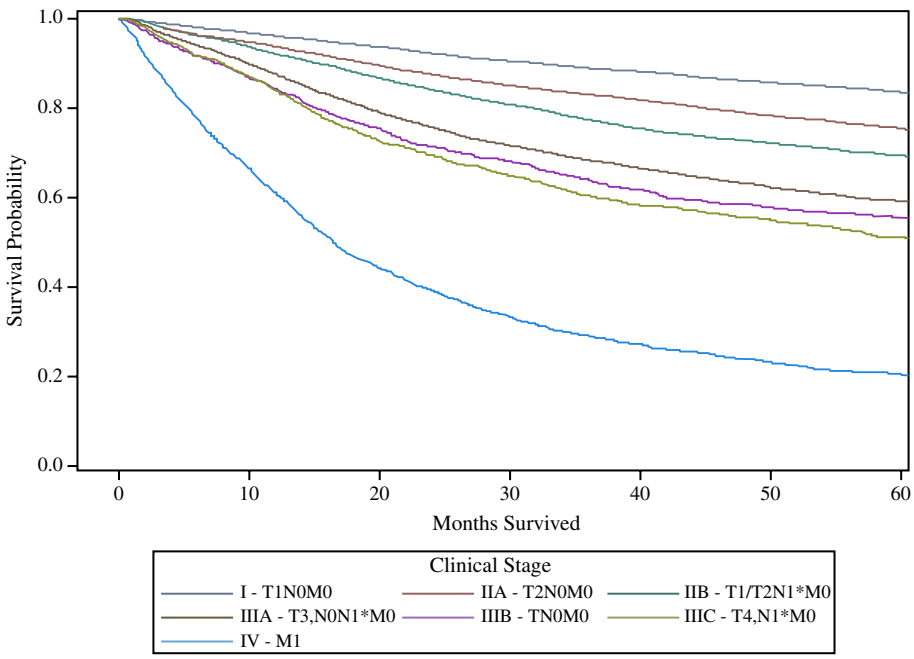

FIG. 1 Five-year overall survival for patients with anal cancer based on the revised American Joint Committee on Cancer Version 9 staging system definitions. Reproduced with permission from the American College of Surgeons, Chicago, IL, USA. The original source for this information is the AJCC cancer staging system (2023).

T3-T4N1M0 to T4N1M0. As the T category for anal cancer is solely determined by tumor size, this finding that larger, node-negative tumors are associated with a worse prognosis compared with smaller, node-positive disease may be representative of the difficulty in managing large primary malignancies, based on the available treatment modalities.

Interestingly, the NCDB data utilized by the AJCC expert panel on anal cancer that informed the Version 9 stage group revisions are reflective of the results demonstrated by the US Gastrointestinal Intergroup Radiation Therapy Oncology Group (RTOG) 98-11 anal cancer trial, reporting a worse prognosis for larger tumors than for node-positive disease.[12,13] Although the use of intensity-modulated radiotherapy (IMRT) has been increasingly implemented over the past decade, the standard treatment course for patients with anal cancer has remained relatively static, primarily consisting of pelvic radiotherapy in combination with 5-fluorouracil-based chemotherapy and mitomycin C.[14] While the use of IMRT in practice has been shown to reduce rates of treatment toxicity associated with receiving radiotherapy, since the radiotherapy dose has not changed substantially, there may be less of an impact of IMRT on improving local control among patients with larger primary tumors.[15] While it is well known that larger tumors are less radiosensitive due to a more hypoxic environment, additional work is needed to identify new treatment strategies for patients with advanced T-category disease. Thus, despite the availability of newer radiotherapy techniques such as IMRT, as well as newer studies assessing alternative chemotherapy combinations and dose escalation for patients with more advanced disease, further efforts are imperative in order to improve survival outcomes for this high-risk patient population.

STAGE 0 ELIMINATED FROM THE AJCC STAGING SYSTEM FOR ANAL CANCER

Lastly, stage 0, defined as in situ (Tis) disease, was removed by the expert panel from the AJCC Version 9 staging system for anal cancer entirely. The rationale for this decision was that Tis lesions of the anal canal are completely intraepithelial, meaning they have not yet crossed the basement membrane and therefore are considered a type of high-grade squamous intraepithelial lesion (HSIL). These lesions are, by definition, not cancer but may progress to true malignancy if not adequately treated. Stage 0 disease represented the Tis category, which is only premalignant and thus not yet a form of invasive malignancy. Additionally, inclusion of Tis lesions in previous AJCC staging system editions has, in some instances, led to patients being erroneously treated with chemoradiation protocols, instead of the more appropriate approach of local ablative procedures, local excision, or the administration of topical fluorouracil or imiquimod as evidenced in the ANal Cancer/HSIL Outcomes Research (ANCHOR) trial.[16] Similarly, National Comprehensive Cancer Network guidelines do not include treatment recommendations for the management of Tis lesions of the anal canal,[17] hence stage 0 disease was also removed from the AJCC Version 9 staging system for anal cancer.

CONCLUSION

Several evidence-based updates were implemented in the AJCC Version 9 staging system for anal cancer based on the evaluation of contemporary survival outcomes among this patient population, as well as additional emerging evidence. These modifications included redefining stage IIB from T3N0M0 to T1-T2N1M0 disease, redefining stage IIIA from T1-T2N1M0 to T3N0-N1M0 disease, redefining stage IIIC from T3-T4N1M0 to T4N1M0 disease, and removing stage 0 disease from the staging system for anal cancer overall. In general, patients with localized anal cancer have excellent oncologic outcomes, however those with higher risk features, such as larger tumor size, have worse survival outcomes. Studies are needed to identify novel therapies to improve survival outcomes for patients with advanced forms of this rare malignancy. Hence, the present changes to the AJCC staging system for anal cancer represent an important step in refining the way we define the extent of disease, which affects cancer care delivery, prognostication, and future research among this population.

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