# Validation and Modification of the American Joint Commission on Cancer 8th Edition Staging System for Patients With Anal Squamous Cell Cancer: A Surveillance, Epidemiology and End Results Analysis

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# Abstract

This study aimed to validate the clinical utility of American Joint Committee on Cancer (AJCC) 8th edition staging system for anal squamous cell cancer (ASCC). Further, Surveillance, Epidemiology, and End Results database (2004–2015) was used to validate the practicability of 8th AJCC stages. Disease-specific survival (DSS) and overall survival (OS) were evaluated using Kaplan-Meier analysis. Hazard ratios (HRs) were calculated using Cox regression analysis. Furthermore, the modification was validated using Kaplan-Meier analysis and calculating the concordance index (C-index). A total of 11891 patients with ASCC were analysed. the 5-year DSSs for stage I, IIA, IIB, IIIA, IIIB, IIIC, and IV were 93.8%, 87.4%, 76.2%, 76.9%, 72.0%, 66.1%, and 34.9%. We found the OS and DSS of IIIA patients showed better than IIB. After hazard analysis, modified IIIA patients showed worse OS and DSS than IIB. C-indexes were increased from 0.612 to 0.636 for DSS and from 0.566 to 0.582 for OS of stage II and III ASCCs. In conclusion, our study validated 8th AJCC staging system as overall suitable classification with a few defects. Thus, we suggested modifications in II and III stages to make it more suitable for ASCCs that could be adopted in clinical practice.


# Introduction

Anal squamous cell cancer (ASCC) is a relatively uncommon malignancy, accounting for approximately 1% of all gastrointestinal cancers in the US[1]. In 2017, there were over 8,200 estimated cases, causing approximately 1,100 deaths which comprised 0.2% of all cancer related deaths[2]. Surgical resection is no longer a routine treatment category for patients with ASCCs; instead, pelvic radiation with concurrent multiagent chemotherapy is considered the standard treatment[3]. Consequently, an updated clinical staging system is effectively needed to evaluate the prognosis in patients with ASCC, considering the novel treatment strategy. The American Joint Committee on Cancer (AJCC) published the first staging system for ASCC in 1988 in the 3rd edition of their manual[4]. The latest 8th edition of the AJCC Staging System was released in 2016[5]. The new edition had two important alterations compared with the 7th edition, including the definition of N stage and clinical categories (Table 1).

Since the 8th edition of the AJCC staging system was formulated, its practicability in ASCC patients has been validated by a limited number of studies. Paolo Goffredo[6] et. al validated the 8th AJCC subclassification of stage II anal cancer, and Eli D. Scher[7] et al. focussed on the prognostic implications of advancing nodal stage through an NCDB analysis. However, there is still no systematic and accurate validation of the accurate prediction of prognosis by the AJCC 8th staging system in patients with ASCC. The aim of the current study was to conduct a pre-specified validation and make a scientific attempt to modify the 8th AJCC staging system within the general ASCC population using a nationally representative public database.

# Materials And Methods

## Retrieval Strategy

The Surveillance, Epidemiology, and End Results (SEER) program collects data from 18 different regions that represent approximately 28% of the US population[2]. It employs the ICD-O-3 for histology coding (SCC: code 8070–8078)[8]. Patients diagnosed with ASCC between 2004 and 2015 were included in the study cohort. The exclusion criteria were as follows: (1) patients without diagnosis of ASCC; (2) patients without pathological diagnosis until autopsy; and (3) patients with incomplete information in the AJCC staging system.

## Study Variables Definition

The AJCC staging system variables included T, N, M, and clinical stages. Demographic variables included patient sex, age at diagnosis, race, and survival status as of 31 December 2016. Age at diagnosis was treated as a continuous variable. Race was classified as White, Black American Indian/Alaska Native, and Asian or Pacific Islander. Clinical characteristics included type of surgery and utilisation of radiation therapy and chemotherapy. Surgery was subclassified into no surgery, local excision (including local tumour destruction and/or excision), and radical resection (including Hartmann's operation, low anterior resection, and abdominal perineal resection). Pathologic characteristics included tumour size, lymph node involvement, and metastases at diagnosis. Tumour size was classified as a continuous variable; tumours sized ≥ 20.0 cm were excluded due to the possibility of errors in the coding process.

## Follow-up Data Definition

The main end-point event in this study was overall-cause death and specific-cause death. The overall survival (OS) was defined as the time from diagnosis to the date of death or when censured at the latest date if patients were still alive. While disease-specific survival (DSS) was defined as the time from diagnosis to the date of cancer-related death or when censured at the latest date if patients were still alive.

## Missing data Definition and Handling

Missing data was definition as ASCC patients with unknown survival months or dead with unknown reason. Further, we consider these data (n = 1422) are missing at random and employed the Multiple Imputation (MI) method via Markov Chain Monte Carlo to handle[9]. MI is a sophisticated but flexible approach for handling missing data and is broadly applicable within the standard statistical software package of R 4.0.1.

## Statistical Analyses

Demographic, clinical, and pathologic data were analysed using summary statistics. The Chi-square test, Student's *t*-test, Kruskal-Wallis test, and Mann-Whitney U test were used for comparisons of categorical and continuous variables, respectively. The Kaplan-Meier (KM) method was used to determine OS and DSS, and the log-rank test was used to calculate statistical significance of comparisons of OS and DSS.

the univariable Cox proportional hazards regression was utilized for the AJCC staging model construction associated with all-cause death and specific causes of death. The alter in AJCC staging systems were showed by Heatmaps. Further, c-indices were used for assessing performance of the staging systems.

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 24.0; SPSS Inc., Chicago, IL, USA) and R 4.0.1. Heatmaps were drawn using Prism software (version 8.0). All tests were two-sided, and a $p$-value < 0.05 was considered statistically significant. The SEER databases are publicly available, and all patient information is de-identified; therefore, this study was granted an exemption from the institutional review board approval.

# Result

### Demographic Data and Clinicopathological Characteristics

This study extracted 13606 patients diagnosed with ASCC from SEER database and excluded 1715 patients with incomplete TNM stage info. A total of 11891 patients diagnosed with ASCC between 2004 and 2015 were included in our study finally. Clinicopathologic data for different 8$^{th}$ AJCC clinical stages are presented in Table 2. There was a higher proportion of men among SEER patients diagnosed with ASCCs. Meanwhile, the main proportion in the SEER cohort was represented by the patients of a White race. Furthermore, for patients with most of the clinical stages among the ASCC patient cohort, no surgical resection was performed (59.1–83.5%), except for those with stage I (32.9%). Except for I stage ASCC patients, the number of ASCC patients who underwent radiation therapy and chemotherapy treatment was not significantly different between the 8$^{th}$ AJCC clinical stages of ASCC patients.

### Disease-specific survival and Overall Survival for different T, N and M Classifications

The 5-year DSS rates was 86.1% for T1, 83.6% for T2, 67.6% for T3, and 62.3% for T4 tumours and the 5-year OS rates was 80.0% for T1, 65.2% for T2, 47.1% for T3 and 42.9% for T4 for according to the AJCC 8$^{th}$ edition staging system. When stratified by the AJCC 7$^{th}$ nodal classification system, DSS did not differ significantly ($\lambda$ = 1.429, $p$ = 0.232) between N1 and N2 nodal status in patients with ASCC but OS differed significantly ($\lambda$ = 4.775, $p$ = 0.029). When evaluated using the AJCC 8$^{th}$ nodal classification system (N0 *vs.* N1), there were significant differences in DSS ($\lambda$ = 466.352, $p$ < 0.001) and OS ($\lambda$ = 273.702, $p$ < 0.001) between the stages (Figure 1).

Furthermore, the comparison between the 5-year DSS rates in patients with $T_xN_+M_0$ stages defined using 7$^{th}$ and 8$^{th}$ editions showed that there was no significant difference in DSS between N1, N2 and N3 among ASCC patients with T1 and T3 according to the AJCC 7$^{th}$, similar with OS (Supplementary 1). In the AJCC 8$^{th}$ M classification, DSS ($\lambda$ = 1219.892, $p$ < 0.001) and OS ($\lambda$ = 1091.599, $p$ < 0.001) also differed significantly.

### AJCC stage groupings

According to the AJCC 8th edition staging system, the 5-year DSS rates were 94.2% for stage I, 86.4% for stage IIA, 74.9% for stage IIB, 79.4% for stage IIIA, 72.2% for stage IIIB, 64.8% for stage IIIC, and 35.4% for stage IV ASCC patients and the 5-year OS rates were 81.7% for stage I, 68.1% for stage IIA, 53.4% for stage IIB, 65.1% for stage IIIA, 50.7% for stage IIIB, 48.5% for stage IIIC, and 21.2% for stage IV ASCC patients (Figure 2a). The new AJCC subclassification of stage II ASCCs into A and B showed a favourable discrimination in DSS ($\lambda$ = 80.833, $p$ < 0.001) and OS ($\lambda$ = 82.121, $p$ < 0.001) between IIA and IIB (Figure 2b). Furthermore, 8th AJCC subclassification of stage III ASCC patients also showed a better differentiation strategy of OS ($\lambda$ = 41.451, $p$ < 0.001) than that of the 7th AJCC (λ = 1.071, $p$ = 0.301) for IIIA *vs.* IIIB (Figure 2c).

## Modification of the 8th AJCC clinical staging system

A few deficiencies were found when we verified the efficacy of discrimination in the 8th AJCC clinical staging system, especially between IIB and IIIA stages. KM analysis showed that the DSS ($\lambda$ = 10.153, $p$ = 0.002) and OS ($\lambda$ = 47.652, $p$ < 0.001) of IIIA ASCC patient showed much better than IIB patients with significant differences. Further, there was no significant difference in OS between IIIB and IIIC ($\lambda$ = 0.037, $p$ = 0.848) (Figure 3a). To identify the impact of deficiencies on the discriminatory value of the system, we calculated univariable Cox proportional hazards for DSS and OS in each of the 8th clinical stages and actual TNM stages among the ASCC patients (Supplementary 2) and made heatmaps (Figure 3b).

Furthermore, we analysed the hazards for actual TNM stage ASCC patients and modified the AJCC 8th clinical staging system (Table 3). The novel AJCC IIB stage was modified as T1N1M0, the IIIA stage was modified as T3N0M0 and T2N1M0, the IIIB stage was modified as T4N0M0 and T3N1M0 and the IIIC stage was modified as T4N1M0, while the corresponding 8th IIB stage was defined as T3N0M0, IIIA stage as T1-2N1M0, IIIB stage as T4N0M0 and IIIC stage as T3-4N1M0.

## Validation of the modified 8th AJCC staging system

The prognostic utility of the 8th AJCC clinical staging system was enhanced after our modifications. ASCC patients experienced worse prognosis as the AJCC stage increased, except that the differences in prognostic outcomes were not significant between IIB and IIIA stage ASCC patients. After the modification, IIIA patients showed logically worse DSS ($\lambda$ = 4.952, $p$ = 0.022) and OS ($\lambda$ = 14.210, $p$ < 0.001) than IIB patients with significant difference. Moreover, the discrimination of OS between IIIB and IIIC patients has been promoted although with no significant difference ($\lambda$ = 1.994, $p$ = 0.120) (Figure 3c).

The C-indices of the different staging systems had been promoted after modifications. For DSS of ASCC patients in the SEER cohort, the C-index of the 8th staging system increased from 0.697 (95%CI: 0.686–0.709) to 0.711 (95%CI: 0.699–0.722) compared with that of the 7th Staging System for all stages of ASCC. For II and III stages ASCC patients, the C-index was also increased from 0.585 (95%CI: 0.571–0.601) to 0.612 (95%CI: 0.597–0.626). The C-index increased significantly after our modification, from 0.612 (95%CI: 0.597–0.626) to 0.636 (95%CI: 0.611–0.645) for II and III stage ASCC patients, and from

0.711 (95%CI: 0.699–0.722) to 0.721 (95%CI: 0.703–0.729) for the entire cohort (the OSs promotion showed in Supplementary 3).

# Discussion

This large, population-based study validated and modified the 8th edition AJCC staging system for patients with ASCC utilising a nationally representative database in the US. The results showed that this new staging system performed well in different T, N, and M stages. Meanwhile, the 8th AJCC clinical staging system was also effective for the main stages, except for the IIB and IIIA stages. Thus, our study modified them by analysing the hazard ratios in different stages. This could be meaningful and favourable for further revision in the AJCC staging system for patients with ASCC.

Compared with the 7th edition, the 8th edition of the AJCC TNM staging system has introduced no changes in the classification of the T and M stages, while there were some revisions done for the N stages. Specific changes to the classification of the N stages included the deletion of N2 and N3 stages, and the new N1a, N1b, and N1c stages were redefined to reflect lymphatic metastasis, which was done according to long-term updated results of the RTOG 98-11 phase III trial for anal carcinoma[10]. However, Eli D. Scher et al.[7] considered that advanced nodal stage as per AJCC 7th edition retained prognostic implications for overall survival (OS) in earlier T stages in the NCDB cohort. Nevertheless, our study found that AJCC 7th N stages performed poorly for OS and DSS among the T1-2 stages in the SEER cohort, especially for N1-2 stages. This discrepancy might be caused by differences in research outcomes and cohorts. Furthermore, our findings indicated that the level of nodal burden did not influence the 5-year OS and DSS rates in patients with T3 primary tumours, especially for N1-2 stages. This phenomenon is also supported by comparable results from an earlier retrospective analysis[11], which revealed that in the setting of N+ disease, those with early (T1-2) tumours had 5-year OS rates of 72.7%, compared to only 39.9% in those with more advanced (T3-4) disease.

The alteration of the 8th AJCC clinical staging system mainly focused on II and III stage ASCC patients. In a previous study[6], the 8th edition AJCC subclassification of stage II anal cancer into A and B was validated as an effective modification in NCDB and SEER cohorts, which coincided with the results obtained in our study. With regard to the subclassification of stage III anal cancer, we found that there was a significant difference in the OS and DSS rates between IIIA and IIIB-C stages ASCC patients, which was superior to the AJCC 7th edition III stage. However, OS rates in ASCC patients between IIIB (T4N0M0) and IIIC (T3-4N1M0) stages did not show significant differences in this study. This result mirrored that of the RTOG 98-11 study, which showed that patients with T4N0 tumours had proportionate 5-year OS rates compared to those with T3-4N+ tumors[12]. Furthermore, our study showed that OS and DSS rates in ASCC patients with IIB and IIIA stages seemed to be inverse in the SEER cohort. In addition, the Kaplan-Meier survival curves between patients with stage IIB and IIIA disease were completely reversed when using the 8th AJCC staging system. From our viewpoint, this situation might have arisen from the advances made in the development of chemoradiotherapy in the last 15 years. In other words, the weight of lymph node

status appears to be overestimated in this modern era of multimodal management, which has also been observed in pancreatic cancer[13] and gallbladder carcinoma[14]. Thus, we modified the substages within IIB and IIIA to maintain a balance between the T and N disease.

After comparing the hazard ratios for AJCC 8$^{th}$ clinical stages and TN categories, we made a new definition that modified T3N0M0 and T2N1M0 as stage IIIA, while T1N1M0 was assigned to stage IIB. As expected, the accuracy of the differentiation between stage IIA and IIIB prognosis was satisfactory after our modification. In part, the reason was that the prognosis in T3 ASCC patients had proved to be much worse than that in T2 patients with a difference of >15% in 5-year OS and DSS, which was also validated by Paolo Goffredo et al.[6] in the NCDB cohort. Furthermore, AJCC 8$^{th}$ N+ stages had a 6-9% decrease of the 5-year OS and DSS rate in T2-3 stage, and this reduction was much lower than the difference between T3 and T2 stages. Moreover, since Nigro et al.[15] proposed radiotherapy and chemotherapy for ASCC patients in 1974, the treatment categories were changed from surgical treatment to a comprehensive treatment using radiotherapy and chemotherapy[16,17]. We found that the number of ASCC patients treated with radiotherapy and chemotherapy was not different in all clinical stages, which meant that nodal stages might have occupied a less important position in grouping prognosis. Meanwhile, the revision of the AJCC 8$^{th}$ staging system mainly focused on nodal stages precisely because of these clinical results. Our study made a simple but very significant modification to ASCC staging based on the AJCC 8$^{th}$ staging system and aimed to improve this classification more accurately and systematically.

There were a few limitations in our study. Firstly, our study were retrospective analyses and unavoidable had inherent imperfection to using such large clinical databases. Some data such as results of pertinent biochemical and genetic laboratory studies could not be included because they were not recorded in the SEER database. In addition, the current SEER database did not provide any information regarding the classification of external iliac involvement in AJCC 8$^{th}$ N stage, which made it impossible to validate N1a, N1b, and N1c. Nevertheless, the SEER cohort were high-volume and well-validated for researchers to analyse epidemiologic and clinical issues on ASCC.

# Conclusions

We validated the effectiveness of alterations in the 8$^{th}$ AJCC staging system for ASCC using a large representative clinical cohort. This study discovered that the new AJCC 8$^{th}$ classification performed well in differentiating between the OS and DSS rates in different stages in ASCC patients. Nevertheless, a few deficiencies were found in the system, including not very accurate stratification of IIIB and IIIC patients and aberrant OS and DSS reversal for stage IIB and IIIA patients. Therefore, we proposed a modified version to obtain more accurate risk stratification, which might be adopted in the next version of the AJCC Staging System.

# Declarations

### Funding

This study was supported by National Natural Science Foundation of China (No. 81702386, 81874184), and the funders had role in study design and data interpretation.

### Competing Interests Statement

The authors have no disclosures or conflicts of interest to declare.

### Ethics approval

Informed consent is waived as SEER is a de-identified, publicly available cancer database.

### Author Contributions Statement

Kaixiong Tao and Peng Zhang put forwards the conceptualization; Yao Lin and Chengguo Li analysis the data; Yao Lin and Xiong Sun did the investigation; Yao Lin and Chengguo Li wrote the main manuscript text and Xin Chen prepared figures 1-3; Tao Wang checked the syntax of manuscript; Kaixiong Tao and Peng Zhang provided the fund; All authors reviewed the manuscript.

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# Tables

**Table 1. American Joint Committee on Cancer (AJCC) 7$^{th}$ and 8$^{th}$ edition staging system for anal squamous cell cancer**

| 7th AJCC Staging System | | 8th AJCC Staging System | |
|---|---|---|---|
| T1 | Tumor 2cm or less in greatest demension | T1 | Tumor 2cm or less |
| T2 | Tumor more than 2cm but not more than 5cm in greatest demension | T2 | Tumor more than 2cm but not more than 5cm |
| T3 | Tumor more than 5cm in greatest demension | T3 | Tumor more than 5cm |
| T4 | Tumor of any size invades adjacent organ(s), such as the vagina, utethra, bladder | T4 | Tumor of any size invades adjacent organ(s), such as the vagina, utethra, bladder |
| N0 | No regional lymph node metastasis | N0 | No regional lymph node metastasis |
| N1 | Metastasis in perirectal lymph node(s) | N1a | Metastasis in inguinal, mesorectal,or internal iliac |
| N2 | Metastasis in unilateral internal iliac and/or inguinal lympg | N1b | Metastasis in external iliac lymph nodes |
| N3 | Matastasis in perirectal and inguinal lymph node(s) and/or bilateral internal iliac and/or inguinal lympg nodes | N1c | Metastasis in external iliac lymph nodes with any N1a nodes |
| M0 | No distant metastasis | M0 | No distant metastasis |
| M1 | Distant metastasis | M1 | Distant metastasis |

| 7th AJCC Staging System | | 8th AJCC Staging System | |
|---|---|---|---|
| I | T1N0M0 | I | T1N0M0 |
| II | T2-3N0M0 | IIA | T2N0M0 |
| IIIA | T1-3N1M0, T4N0M0 | IIB | T3N0M0 |
| IIIB | T4N1M0, TanyN2M0, TanyN3M0 | IIIA | T1-2N1M0 |
| IV | TanyNanyM1 | IIIB | T4N0M0 |
| | | IIIC | T3-4N1M0 |
| | | IV | TanyNanyM1 |

**Table 2. Demographic, clinical, and pathologic characteristics for the entire cohort**

| Patient characteristics | AJCC 8th Stage of ASCC | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I | IIA | IIB | IIIA | IIIB | IIIC | IV | *p* value |
| n | 2711 | 3785 | 936 | 1696 | 531 | 1449 | 783 | |
| **Demographic** | | | | | | | | |
| Age at diagnosis, years | | | | | | | | <0.001 |
| Mean ± SD | 59.74 ± 12.706 | 61.65 ± 12.818 | 61.74 ± 13.708 | 59.88 ± 12.056 | 62.21 ± 13.561 | 58.77 ± 12.503 | 61.11 ± 12.778 | |
| Sex | | | | | | | | <0.001 |
| Female | 1568 (57.9) | 2368 (62.6) | 548 (58.5) | 1148 (67.7) | 405 (76.3) | 947 (65.4) | 490 (62.6) | |
| Male | 1143 (42.1) | 1417 (37.4) | 388 (41.5) | 548 (32.3) | 126 (23.7) | 502 (34.6) | 293 (37.4) | |
| Marital status at diagnosis | | | | | | | | <0.001 |
| Married | 1181 (43.6) | 1605 (42.4) | 324 (34.6) | 702 (41.4) | 198 (37.3) | 525 (36.2) | 277 (35.4) | |
| Divorced | 384 (14.2) | 610 (16.1) | 163 (17.4) | 310 (18.3) | 100 (18.8) | 251 (17.3) | 161 (20.6) | |
| Single (never married) | 858 (32.0) | 1086 (28.7) | 321 (34.3) | 485 (28.6) | 136 (25.6) | 514 (35.5) | 250 (31.9) | |
| Widowed | 278 (10.3) | 484 (12.8) | 128 (13.7) | 199 (11.7) | 97 (18.3) | 159 (11.0) | 95 (12.1) | |
| Race | | | | | | | | <0.001 |
| White | 2348 (86.6) | 3342 (88.3) | 794 (84.8) | 1451 (85.6) | 471 (88.7) | 1206 (83.2) | 650 (83.0) | |
| Black | 294 (10.8) | 356 (9.4) | 125 (13.4) | 195 (11.5) | 49 (9.2) | 206 (14.2) | 103 (13.2) | |
| American Indian/Alaska Native | 66 (2.4) | 82 (2.1) | 14 (1.6) | 48 (2.8) | 10 (2.0) | 34 (2.5) | 30 (3.8) | |
| Asian or Pacific Islander | 3 (0.1) | 5 (0.2) | 3 (0.2) | 2 (0.1) | 1 (0.1) | 3 (0.1) | 0 (0.0) | |
| **Clinical and Pathologic** | | | | | | | | |
| Surgery primary site | | | | | | | | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| None | 891 (32.9) | 2236 (59.1) | 636 (67.9) | 1198 (70.6) | 348 (65.5) | 1174 (81.0) | 654 (83.5) | |
| Local excision | 1773 (65.4) | 1387 (36.6) | 226 (24.1) | 428 (25.2) | 48 (9.0) | 188 (13.0) | 93 (11.9) | |
| APR | 47 (1.7) | 162 (4.3) | 74 (7.9) | 70 (4.1) | 125 (23.5) | 87 (6.0) | 36 (4.6) | |
| Radiation therapy | | | | | | | | <0.001 |
| Yes | 1592 (58.7) | 2975 (78.6) | 767 (81.9) | 1458 (86.0) | 404 (76.1) | 1182 (81.6) | 583 (74.5) | |
| Chemotherapy | | | | | | | | 0.815 |
| Yes | 2166 (79.9) | 2988 (78.9) | 743 (79.4) | 1359 (80.1) | 429 (80.8) | 1136 (78.4) | 624 (79.7) | |
| Grade of differentiated | | | | | | | | <0.001 |
| Well differentiated; Grade I | 688 (25.4) | 566 (15.0) | 160 (17.1) | 165 (9.7) | 56 (10.5) | 137 (9.5) | 36 (4.6) | |
| Moderately differentiated; Grade II | 1310 (48.3) | 1902 (50.3) | 498 (53.2) | 793 (46.8) | 265 (49.9) | 703 (48.5) | 326 (41.6) | |
| Poorly differentiated; Grade III | 695 (25.6) | 1275 (33.7) | 274 (29.3) | 721 (42.5) | 207 (39.0) | 600 (41.4) | 411 (52.5) | |
| Undifferentiated; anaplastic; Grade IV | 18 (0.7) | 42 (1.1) | 4 (0.4) | 17 (1.0) | 3 (0.6) | 9 (0.6) | 10 (1.3) | |
| Tumor size, cm | | | | | | | | <0.001 |
| Mean ± SD | 1.37 ± 0.578 | 3.59 ± 0.923 | 6.90 ± 1.906 | 3.36 ± 1.202 | 5.74 ± 3.179 | 6.98 ± 2.922 | 5.64 ± 2.935 | |

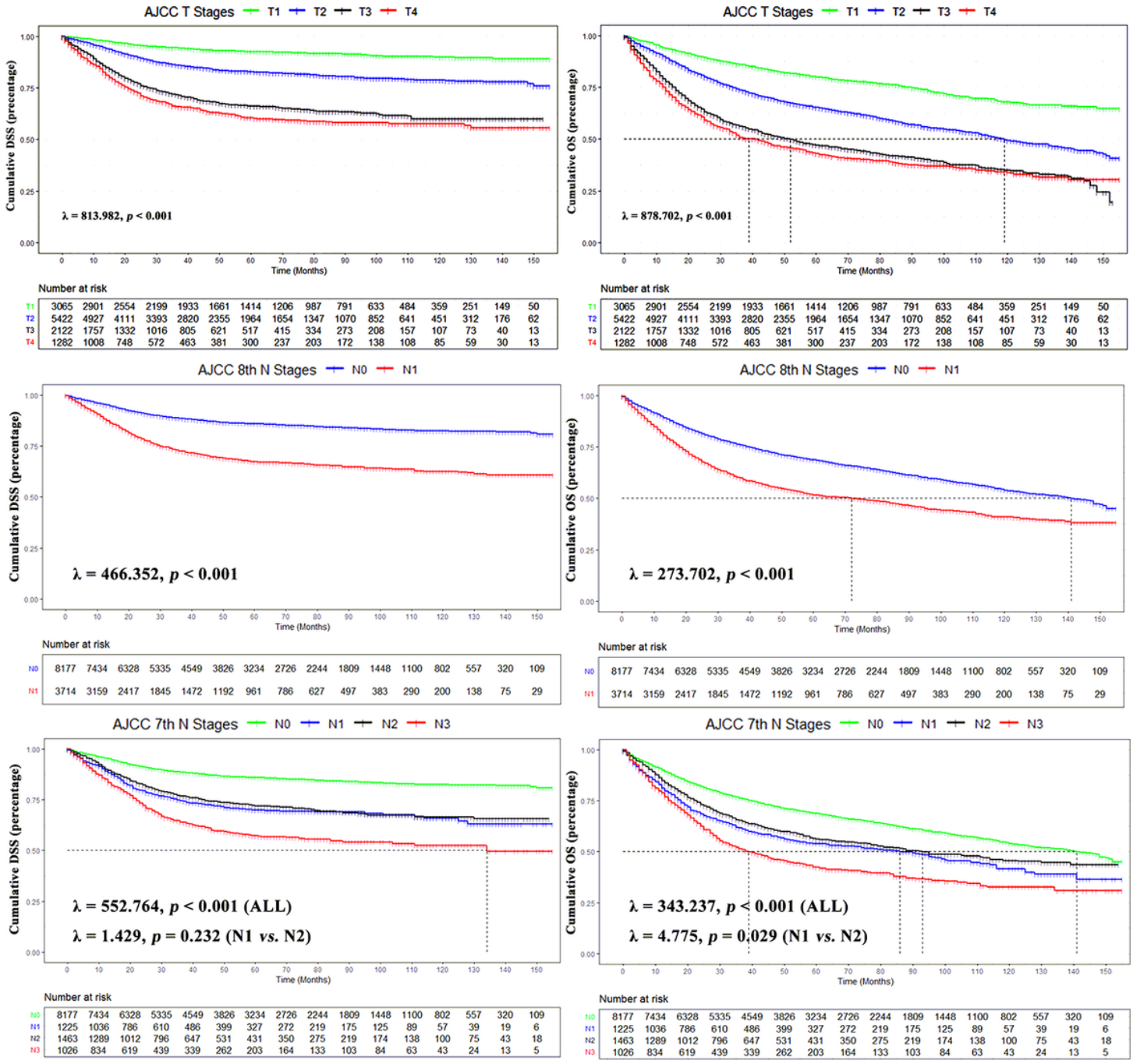
**Table 3 Univariable Cox regression analysis of disease-specific survival (DSS) and overall survival (OS)**

| Variables | DSS | | OS | |
|---|---|---|---|---|
| | Univariables HR (95%CI) | *p* value | Univariables HR (95%CI) | *p* value |
| T stage | | | | |
| T1 | ref. | | ref. | |
| T2 | 2.379 (2.045-2.766) | <0.001 | 1.885 (1.726-2.059) | <0.001 |
| T3 | 5.276 (4.510-6.173) | <0.001 | 3.284 (2.980-3.619) | <0.001 |
| T4 | 6.371 (5.399-7.518) | <0.001 | 3.655 (3.286-4.065) | <0.001 |
| AJCC 8th N stage | | | | |
| N0 | ref. | | ref. | |
| N1 | 2.523 (2.313-2.753) | <0.001 | 1.662 (1.564-1.767) | <0.001 |
| AJCC 7th N stage | | | | |
| N0 | ref. | | ref. | |
| N1 | 2.319 (2.039-2.636) | <0.001 | 1.622 (1.478-1.779) | <0.001 |
| N2 | 2.111 (1.869-2.383) | <0.001 | 1.416 (1.296-1.547) | <0.001 |
| N3 | 3.469 (3.072-3.918) | <0.001 | 2.133 (1.944-2.341) | <0.001 |
| M stage | | | | |
| M0 | ref. | | ref. | |
| M1 | 5.729 (5.127-6.401) | <0.001 | 3.912 (3.583-4.270) | <0.001 |
| AJCC 8th Clinical stage | | | | |
| I | ref. | | ref. | |
| IIA | 2.310 (1.924-2.775) | <0.001 | 1.879 (1.701-2.076) | <0.001 |
| IIB | 4.423 (3.612-5.648) | <0.001 | 2.644 (2.387-3.245) | <0.001 |
| IIIA | 3.628 (2.986-4.407) | <0.001 | 1.977 (1.758-2.224) | <0.001 |
| IIIB | 5.226 (4.126-6.620) | <0.001 | 3.153 (2.723-3.654) | <0.001 |
| IIIC | 6.516 (5.406-7.853) | <0.001 | 3.294 (2.942-3.687) | <0.001 |
| IV | 16.939 (14.040-20.435) | <0.001 | 7.656 (6.809-8.609) | <0.001 |
| AJCC 7th Clinical stage | | | | |

| | | | | |
|---|---|---|---|---|
| I | ref. | | ref. | |
| II | 2.755 (2.311-3.285) | <0.001 | 2.082 (1.891-2.291) | <0.001 |
| IIIA | 4.297 (3.527-5.234) | <0.001 | 2.519 (2.239-2.833) | <0.001 |
| IIIB | 5.277 (4.410-6.314) | <0.001 | 2.676 (2.408-2.973) | <0.001 |
| IV | 16.878 (13.990-20.362) | <0.001 | 7.631 (6.787-8.580) | <0.001 |

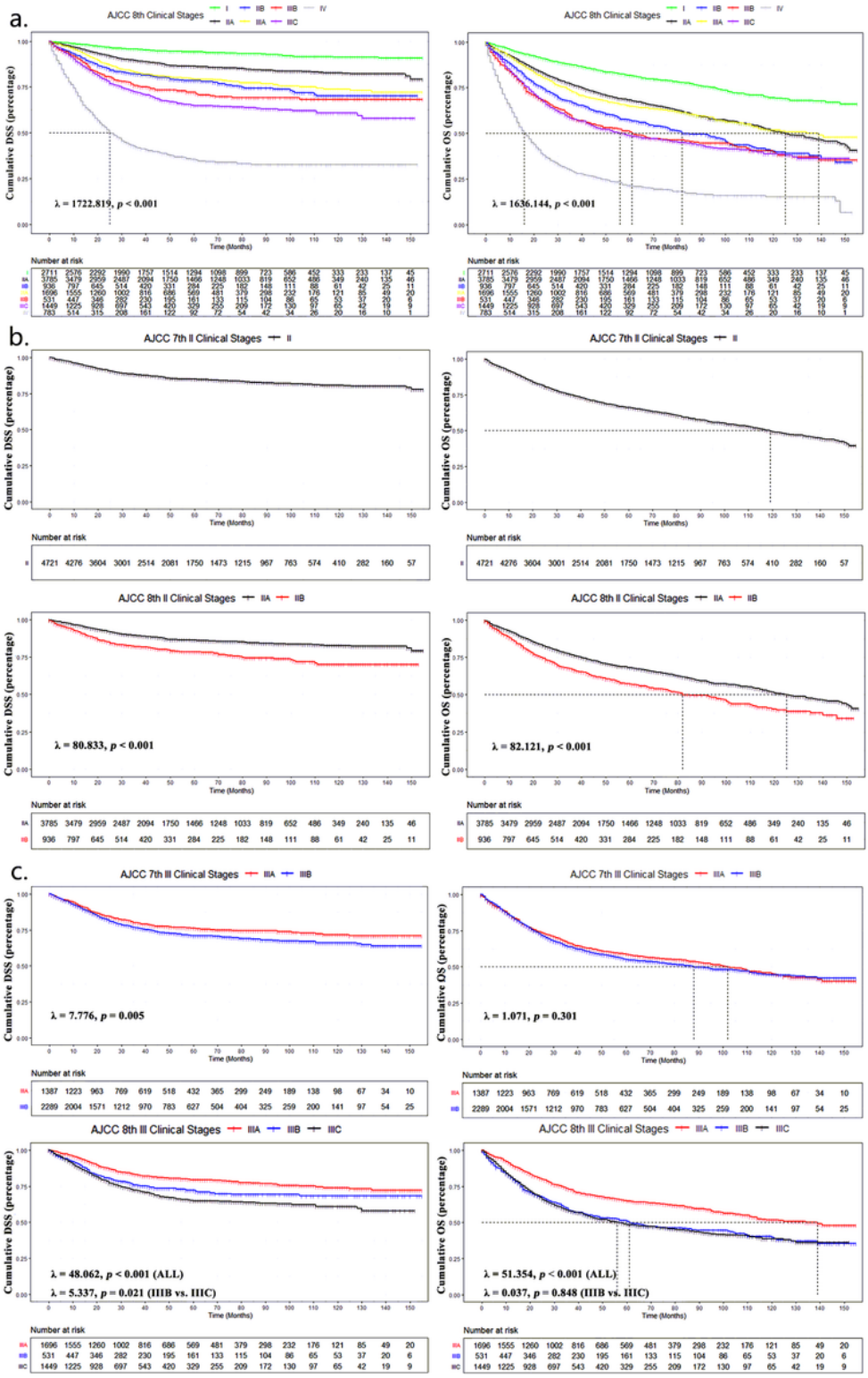
HR hazard ratio, CI confidence interval.

# Figures



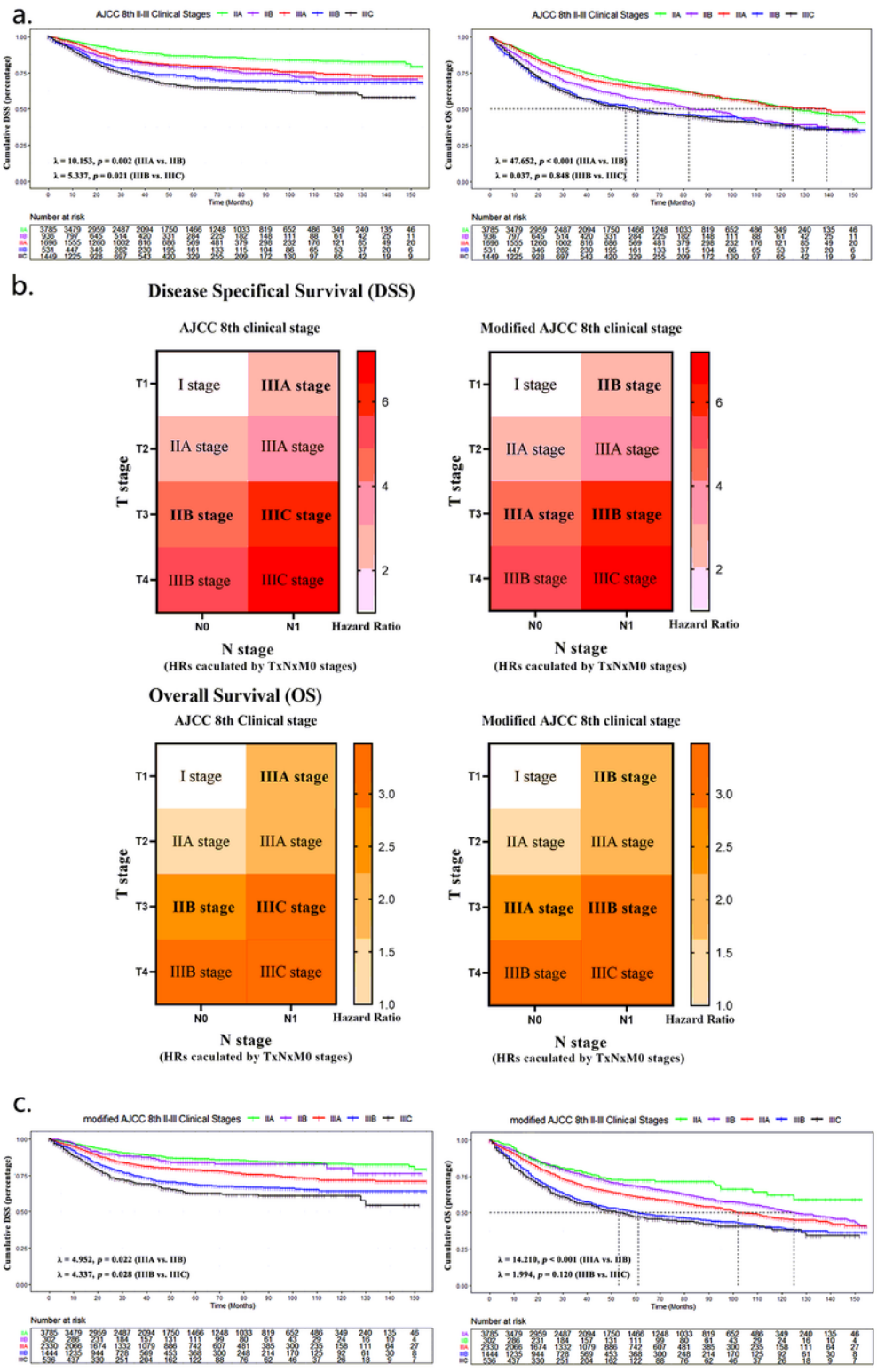

## Figure 1

Kaplan-Meier curves of disease-specific survival and overall survival for AJCC 8th edition T stages and AJCC 7th and 8th edition N stages in the SEER cohort.




## Figure 2

Kaplan-Meier curves of disease-specific survival and overall survival for (a) AJCC 8th edition clinical stages, (b) AJCC 7th & 8th edition II stages and (c) AJCC 7th & 8th edition III stages in the SEER cohort.




## Figure 3

(a) Kaplan-Meier curves of disease-specific survival and overall survival for AJCC 8th II-III stages in the SEER cohort. (b) Hazards heatmaps of disease-specific survival and overall survival for original/modified AJCC 8th edition clinical stages. The depths of color represent values of hazards (the deeper, the higher). (c) Kaplan-Meier curves of disease-specific survival and overall survival for modified AJCC 8th II-IIIA stages in the SEER cohort.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementary1.docx
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- Supplementary3.docx