# Survival Outcomes and Prognostic Staging in Locally Advanced Breast Cancer Patients Receiving Radiotherapy: A Single Center Experience

Yasemin SENGUN, Timur KOCA, Nina TUNCEL, Aylin Fidan KORCUM

Akdeniz University, Faculty of Medicine, Department of Radiation Oncology

**ABSTRACT**

The American Joint Committee on Cancer (AJCC) 8th edition prognostic staging was introduced to improve breast cancer staging by incorporating factors like hormone receptor status and human epidermal growth factor receptor-2 (HER2) expression. This study assesses its effectiveness in locally advanced breast cancer (LABC). A total of 557 patients with locally advanced breast cancer (Stage III) were re-evaluated using prognostic staging. Overall survival (OS), disease-free survival (DFS), and distant metastasis free survival (DMFS) rates were evaluated using the Kaplan-Meier method, and the log-rank test was employed to compare outcomes between anatomic and prognostic staging. According to restaging 34.5% of patients remained in the same stage, while 55.8% were downstaged, and 9.7% were upstaged. When patients reassigned using prognostic staging patients classified as stage IIA showed improved OS rates compared to those in stages IIIA, IIIB, and IIIC ($p< 0.001$ for each). Patients with prognostic stage IIA had better DFS compared to IIIA, IIIB ($p= 0.003$, and $p< 0.001$, respectively). Both anatomic and prognostic staging were found to significantly impact OS in patients with Luminal-A tumors ($p= 0.008$ and $p= 0.001$, respectively), whereas neither anatomic nor prognostic stage had any impact on triple negative subgroup. When stage IIIA patients restaged, downstaged individuals showed better OS than those who stayed at the same stage or were upstaged ($p= 0.01$ and $p= 0.02$, respectively). This study highlights the prognostic staging system's superiority over anatomic staging in predicting survival outcomes for LABC, and the use of the prognostic staging system for more personalized treatment strategies.

**Keywords:** Breast cancer, Radiotherapy, Anatomic staging, Prognostic staging

## INTRODUCTION

Breast cancer is the most frequently occurring type of cancer among women.[1] With the advent of widespread breast cancer screening, more patients are being detected at earlier stages, leading to a decrease in the number of cases detected at locally advanced stages.[2,3] Using the multimodal treatment approach -comprising surgery, radiotherapy, and systemic therapies such as chemotherapy, hormone therapy, and targeted agents- is improved the survival outcomes in patients with locally advanced breast cancer (LABC).[4] Neoadjuvant chemotherapy became standard treatment for LABC by its added benefit of increasing likelihood of breast-conserving surgery (BCS) by reducing tumor size, besides improving survival rates.[5-8]

Since, the staging system was introduced by the AJCC (American Joint Committee on Cancer) in 1977, breast cancer staging has relied on anatomic factors tumor size, lymph node involvement, and metastasis using the TNM system.[9] However, survival outcomes in LABC vary widely, and the TNM system may not fully capture the biological heterogeneity of the disease.[10,11]

Integrating biomarkers like estrogen (ER), progesterone receptors (PR), and human epidermal growth factor receptor2 (HER2) into breast cancer staging has been a significant advancement in cancer management.[12] These biomarkers provide critical information about tumor biology, helping tailor treatment plans and improve prognostic accuracy.[13] ER/PR-positive cancers generally have a better prognosis and respond well to hormonal therapies like tamoxifen or aromatase inhibitors.[14] HER2-positive cancers are more aggressive but respond to targeted therapies like trastuzumab, pertuzumab, tucatinib, lapatinib.[15-18] Despite ongoing research, there is still a critical need for effective treatment options for triple-negative breast cancer, which has the poorest prognosis among breast cancer subtypes.[19]

The risk score analysis using tumor grade and receptor status demonstrated that, within the same anatomic stage, patients with ER-positive breast cancer had the best outcomes, whereas those with triple-negative disease had the poorest outcomes.[20] Furthermore, several studies have suggested that biomarker-integrated models offer better predictive value for breast cancer outcomes, which highlighted the need for a new staging system that includes these additional factors.[21,22] The 8th edition of the American Joint Committee on Cancer (AJCC) staging system introduced a prognostic staging model that integrates key biological markers such as ER, PR, HER2 status, and tumor grade, as well as Oncotype multi-gene assay for early stage, T1-2N0M0, ER+, HER2- tumors.[23] The hypothesis of our study is that this new prognostic system provides a more accurate reflection of survival outcomes in LABC compared to anatomic staging alone, by offering better patient stratification based on both anatomic and biological factors.

## PATIENTS AND METHODS

### *Study Design and Patient Population*

This retrospective study evaluated 557 female patients diagnosed with locally advanced breast cancer who received radiotherapy at our clinic between 2000 and 2019. Patients were included if they were diagnosed with locally advanced disease, defined as stage IIIA-IIIC according to the 8th Edition of the AJCC Cancer Staging Manual, TNM classification. Exclusion criteria included early-stage breast cancer (T1-2N0-1, T3N0), metastatic disease at diagnosis, male patients, and those for whom HER2, ER, PR status, or tumor grade—required for prognostic staging—were not available.

### *Diagnosis and Staging and Restaging*

Diagnosis was pathologically confirmed for all patients. Tumors were staged according to 8th Edition of the AJCC Cancer Staging Manual, which incorporates tumor size (T), nodal involvement (N), and presence of distant metastases (M). Clinical staging was determined based on retrospectively collected data from a combination of clinical and imaging evaluations, including physical examination, mammography, breast ultrasonography, magnetic resonance imaging (MRI), and positron emission tomography (PET). Following initial TNM staging, tumors were restaged according to the AJCC 8th Edition Prognostic Staging System, with integration of histologic grade, hormone receptor status (ER, PR), and HER2 status.[23] When the prognostic stage was higher than the anatomic TNM stage, the cases were classified as upstaged. Conversely, if the prognostic stage was lower, they were considered downstaged. Cases where both stages were identical were defined as stage unchanged.

### *Histopathological Evaluation*

The histopathological evaluation involved examining the tissue samples obtained from surgery or biopsy to assess various tumor characteristics. These included the type of breast cancer, the size of the tumor, and the extent of lymph node involvement. The status of estrogen receptor and progesterone receptor was determined through immunohistochemical (IHC) testing, with receptor positivity defined as cases where 1% or more of the cells showed nuclear staining.[24] HER2 status was also assessed, either through immunohistochemistry or fluorescent in situ hybridization (FISH), and HER2 was considered positive if it scored 3+ on immunohistochemistry or showed gene amplification on FISH.[25]

Based on these results, the tumors were classified into molecular subtypes: Luminal A, Luminal B,

HER2-enriched, or triple-negative breast cancer.[26] Additionally, the grade of the tumor was determined using the Nottingham grading system. Other important features, such as extra nodal extension (tumor spread beyond the lymph node capsule), lympho-vascular invasion (tumor cells in blood or lymph vessels), and perineural invasion (tumor growth around nerves), were also recorded.

### *Treatment Protocol*

All patients received standard multimodal treatment, including surgery, radiotherapy, and systemic therapy -neoadjuvant or adjuvant chemotherapy, hormonotherapy, and targeted therapy- based on molecular subtypes and clinical guidelines. Radiotherapy was administered to chest wall or whole breast and regional lymph nodes as indicated, 50 Gy in 25 fractions, and an additional dose of 10 Gy administered to tumor bed in 5 fractions, Fractionation schedules adapted to patient characteristics and tumor staging. Surgical interventions included mastectomy or breast-conserving surgery, depending on tumor response to neoadjuvant therapy, surgeon's decision, and patient preference.

### *Follow-Up and Outcome Measures*

Patients' records were reviewed for regular clinical assessments and imaging to monitor for disease recurrence. The primary outcome measures included overall survival (OS), disease-free survival (DFS), and distant metastasis-free survival (DMFS). Survival was defined as the time from diagnosis to death or the last follow-up. DFS was defined as the time from diagnosis to local or distant recurrence, and DMFS was defined as the time to the first occurrence of distant metastasis.

### *Ethical Considerations*

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (approval number: KAEK-429; 24.05.2023) Due to the retrospective nature of the study, informed consent was waived by the ethics committee.

**Table 1.** Molecular and histopathologic characteristics of the tumor

| **Histopathology** | **n(%)** |
|---|---|
| Invasive Ductal Carcinoma | 436 (78.3) |
| Invasive Lobular Carcinoma | 36 (6.5) |
| Infiltrative Ductal Carcinoma | 19 (3.4) |
| Mixed Type | 42 (7.5) |
| Other | 24 (4.3) |
| Molecular Subtype | |
| Luminal A | 276 (49.6) |
| Luminal B | 169 (30.3) |
| Triple Negative | 60 (10.8) |
| HER2-enriched | 52 (9.3) |
| ER Status | |
| Positive | 415 (74.5) |
| Negative | 142 (25.5) |
| PR Status | |
| Positive | 370 (66.4) |
| Negative | 187 (33.6) |
| HER2 Status | |
| Positive | 182 (32.7) |
| Negative | 375 (67.3) |
| Grade | |
| 1 | 22 (4) |
| 2 | 301 (54) |
| 3 | 234 (42) |
| Lympho-vascular Invasion | |
| Yes | 291 (52.2) |
| No | 164 (29.5) |
| Unknown | 102 (18.3) |
| Extra Nodular Extension | |
| Yes | 224 (40.2) |
| No | 153 (27.5) |
| Unknown | 180 (32.3) |
| Perineural Invasion | |
| Yes | 88 (15.8) |
| No | 258 (46.3) |
| Unknown | 211 (37.9) |

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize the baseline characteristics of the patients, including age, tumor size, nodal involvement, receptor status, molecular subtype, and treatment received. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. Survival outcomes were analyzed using the

**Table 2.** Distribution of patients by clinical and pathological staging of tumor size (T) and lymph node (N) involvement

| | cN0 | cN1 | cN2 | cN3 | Total for cT Stage n (%) |
|---|---|---|---|---|---|
| **cT0** | - | - | 1 | 1 | 2 (0.4%) |
| **cT1** | - | - | 53 | 24 | 77 (13.8%) |
| **cT2** | - | - | 183 | 77 | 260 (46.7%) |
| **cT3** | - | 50 | 51 | 41 | 142 (25.5%) |
| **cT4** | 10 | 20 | 25 | 21 | 76 (13.6%) |
| **Total for cN stage** | 10 | 4 | 313 | 164 | 557 |
| | **pN0** | **pN1** | **pN2** | **pN3** | **Total for pT Stage** |
| **pT0** | 36 | 7 | 7 | 3 | 53 (9.5%) |
| **pT1** | 14 | 27 | 61 | 18 | 120 (21.5%) |
| **pT2** | 7 | 12 | 156 | 73 | 248 (44.5%) |
| **pT3** | 1 | 32 | 26 | 39 | 98 (17.6%) |
| **pT4** | 6 | 8 | 13 | 11 | 38 (6.8%) |
| **Total for pN stage** | 64 | 86 | 263 | 144 | 557 |

Kaplan-Meier method, and differences in survival between groups were compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

### *Characteristics of patients*

The study included 557 patients aged 26 to 86 years, with a median age of 49. Approximately half of the patients were premenopausal (50.1%), while 45.1% were postmenopausal and 4.8% were perimenopausal. The predominant histological subtype was invasive ductal carcinoma, and Luminal A was the most prevalent molecular subtype. Tumor characteristics, including receptor status, tumor grade, lympho-vascular invasion, extra nodal extension, perineural invasion, and molecular subtypes, are summarized in Table 1. Clinical and pathological T and N stages are detailed in Table 2.

### *Restaging According to Prognostic Staging*

Based on anatomic staging, 60.7% of the patients were classified as stage IIIA, 9.9% as stage IIIB, and 29.4% as stage IIIC. When restaged using the AJCC 8th edition prognostic system, 4.5% staged as stage IB, 25.1% were categorized as stage IIA, 1.8% as stage IIB, 23.7% as stage IIIA, 33.8% as stage IIIB, and 11.1% as stage IIIC. The findings indicated that 34.5% of the patients remained in the same stage, while 9.7% were upstaged, and 55.8% were downstaged. Notably, 66% of Luminal A and Luminal B tumors were downstaged, 60% of TNBC tumors were upstaged. In patients with anatomic stage IIIA, those who were assigned to lower prognostic stage had better overall survival than those who stayed at the same stage or were upstaged ($p= 0.01$ and $p= 0.02$ respectively). However, this difference was not observed in patients with anatomic stage IIIB or IIIC.

### *Survival Outcomes*

The median follow-up period for the study was 83 months (range: 10–292 months). The 5-year OS rate was 83%, and the 10-year OS rate was 67%. The 5-year DFS rate was 74%, while the 10-year DFS rate was 61%. The OS and DFS categorized by both anatomic and prognostic staging, are detailed in Table 3.

According to the anatomic staging, patients in stage IIIA had significantly higher OS rates than those in stages IIIB and IIIC ($p< 0.009$ and $p<0.001$, respectively). However, there was no significant difference between patients in stages IIIB

**Table 3.** Overall and disease-free survival rates by anatomic and prognostic staging (AJCC 8th edition)

| | 5-year Overall survival (%) | 5-year Disease-free survival (%) | 10-year Overall survival (%) | 10-year Disease-free survival (%) |
|---|---|---|---|---|
| **Anatomic stage** | | | | |
| Stage IIIA | 88 | 78 | 74 | 67 |
| Stage IIIB | 82 | 65 | 52 | 49 |
| Stage IIIC | 74 | 69 | 56 | 53 |
| **Prognostic stage** | | | | |
| Stage IB | 96 | 83 | 79 | 74 |
| Stage IIA | 95 | 85 | 81 | 76 |
| Stage IIB | 89 | 90 | 89 | 90 |
| Stage IIIA | 83 | 71 | 65 | 53 |
| Stage IIIB | 77 | 68 | 59 | 53 |
| Stage IIIC | 68 | 70 | 51 | 64 |

and IIIC. Regarding DFS, patients in anatomic stage IIIA had significantly better survival rates than those in anatomic stage IIIC (p= 0.01). DFS rates did not significantly differ between patients with stage IIIB and IIIC cancer. Patients who have anatomic stage IIIA cancer have better distant metastasis-free survival rates compared to those with stage IIIB and stage IIIC (p= 0.009 and p= 0.007, respectively). There was no significant difference in outcomes between patients with stage IIIB and stage IIIC cancer.

### *Survival Outcomes according to prognostic staging*

Patients classified as stage IIA according to prognostic staging had significantly better OS compared to those in stages IIIA, IIIB, and IIIC ($p < 0.001$, for each). No statistically significant difference was observed between other prognostic stage groups. Patients with prognostic stage IIA had superior disease-free survival compared to those in stages IIIA and IIIB (p= 0.03, p< 0.01, respectively). Furthermore, stage IIA patients also showed better distant metastasis-free survival rates compared to patients in stages IIIA and IIIB (p= 0.04 and p= 0.01, respectively).

### *Survival Outcomes According to Molecular Subgroups*

The study also examined the survival outcomes based on different molecular subgroups. The results showed that anatomic and prognostic staging significantly impacted the OS of patients with Luminal A tumors (p= 0.008 and p= 0.001, respectively). Notably, in this subgroup, DFS showed a significant association with prognostic staging but not with anatomic staging (p= 0.028 and p= 0.093, respectively). In the Luminal B molecular subtype, the anatomic staging significantly affected OS and DFS (p= 0.001 and p= 0.019, respectively). However, the prognostic staging did not significantly impact any survival parameter in this group. For patients with TNBC neither OS nor DFS varied significantly between anatomic and prognostic staging. Similarly, among those with HER2-enriched tumors, no significant difference between the two staging, indicating that the reclassification did not alter survival outcomes in these subgroups.

## DISCUSSION

Although the reduced the incidence of locally advanced breast cancer, it remains associated with poorer prognosis compared to the early stage breast cancer.[27] The 15-year overall survival rate for stage IIIA breast cancer patients was 50%, while it was 23% for those with stage IIIB disease.[28] In a study of 2137 patients with stage III breast cancer, 10-year overall survival rates were 65.1% for stage IIIA, 41.2% for stage IIIB, and 26.7% for stage IIIC.[29] Regarding survival rates of locally advanced breast cancer, Yang et al. reported that the 5-year OS rates

among patients with stage IIIC breast cancer differ significantly between anatomic and prognostic staging, with survival rates of 63.5% and 50%, respectively.[30] In our cohort anatomic stage IIIC had OS rate of 74% while, prognostic stage IIIC had 68%. These findings underscore the potential utility of guiding treatment decisions on this group of patients with relatively worse survival rates, as it provides a more on spot assessment compared to traditional anatomic staging.

In a restaging analysis of the SEER database, over 10,000 cases of locally advanced breast cancer were examined, revealing that 33% of patients were downstaged and 41% were upstaged upon re-evaluation.[31] Similar to our findings upstaging was predominantly observed in the triple-negative subgroup, whereas downstaging was more frequently seen in the hormone receptor-positive group.[31] In anatomical staging, there were significant differences in survival outcomes between stage IIIA and IIIB, as well as between IIIA and IIIC. Although, no significant difference was observed between anatomic stages IIIB and IIIC. prognostic staging revealed a significant difference between these two stages.[31] Our results were consistent with these findings.

After the introduction of the new prognostic staging system, a validation study involving 3,327 patients with stage I-IIIC breast cancer from the MD Anderson Cancer Center and 57,466 patients with stage I-IV breast cancer from the California Cancer Center demonstrated that the prognostic staging system has a higher c-index, indicating a more accurate predictive model compared to traditional staging methods.[32] Furthermore, the Cox proportional hazards model showed that the clinical prognostic stage exhibited significantly greater discriminatory power than the anatomic stage.[33] Notably, pairwise comparisons revealed that this improvement was especially pronounced in patients with clinical prognostic stage I and stage III disease, indicating a more precise prediction of outcomes in these specific groups.[33]

The superiority of prognostic staging system in predicting breast cancer prognosis has been repeatedly confirmed in various studies encompassing different patient subgroups.[34-40] This staging system better reflects outcomes across various molecular subtypes and supports the development of tailored treatment plans, leading to improved cost-effectiveness.[31,41] Additionally, the multivariate analysis of SEER database cases with LABC confirmed that prognostic staging serves as an independent prognostic indicator, alongside other treatment variables (including breast surgery, lymph node dissection, chemotherapy, and radiotherapy) and patient-related factors (such as race and marital status).[31]

Looking at molecular subtypes, triple-negative breast cancer (TNBC) is known for predominantly affecting younger patients and having poorer survival outcomes compared to other subtypes.[42] In a large cohort analysis of TNBC cases using the SEER database, more than half of the patients were upstaged when reclassified based on prognostic staging.[43] In accordance with our findings, survival analyses did not reveal a significant difference between anatomic and prognostic staging systems in TNBC.[43] Similarly, other studies focusing on TNBC patients found that prognostic staging did not show significant differences, highlighting the need for additional molecular or genetic markers to improve prognostic stratification, which has not yet been adequately addressed.

Luminal A breast cancer is characterized by its favorable prognosis and responsiveness to endocrine therapies due to hormone receptor positivity.[44] A study investigating prognostic staging particularly in this group, found that among the cases that are reassigned, 170 of 175 were downstaged, while only 5 cases were upstaged.[45] Although no significant differences in 5-year OS were found between anatomic stage groups, prognostic staging was able to demonstrate such differences.[45] The present study also highlights the ability of prognostic staging to reveal distinct outcomes in Luminal A tumors.

Investigating Luminal B breast cancer, when patients initially classified as anatomic Stage III were reassigned to prognostic Stage II or III, those reclassified as prognostic Stage II demonstrated significantly better survival outcomes (DFS and OS) compared to those reclassified as prognostic Stage III.[46] However, this survival difference was

not demonstrated for patients who were reassigned from anatomic Stage I or II.[46] Our results align with these findings as prognostic staging did not reveal any significant survival differences, whereas anatomic staging showed significant variations in survival outcomes for different stages of Luminal B patients. In another study, Luminal B-like (HER2) patients initially classified as anatomic Stage III were reassigned to prognostic Stage II or III. Those reassigned to Stage II had significantly better 5-year disease-specific survival (DSS) and OS.[47] Among patients reassigned from anatomic Stage II, significant differences were found in DSS but not OS, while no significant differences were observed in those reassigned from anatomic Stage I.[47] This corroborates our findings, as patients in our cohort reassigned from stage III to lower stages exhibited better survival.

To better identify the patient subgroup that would benefit the most from prognostic staging, a retrospective study examined its significance in patients with internal mammary lymph node metastases (cN3b; anatomic stage IIIC).[48] The study found that 61% of patients were downstaged when prognostic staging was applied. Furthermore, those downstaged to prognostic stage IIIA or IIIB demonstrated higher survival rates than those who remained in stage IIIC.[48]

### *Limitations of the study*

The main limitations of this study include its retrospective design, which may introduce bias due to incomplete or inconsistent data, and the use of single-institution data, limiting the generalizability of the findings to other populations or clinical settings.

## Conclusion

Our study holds value as it represents the results focusing exclusively on patients with locally advanced breast cancer who received adjuvant radiotherapy. The findings of the study confirm the hypothesis that the AJCC 8th edition's prognostic staging system provides more accurate patient stratification compared to traditional anatomic staging, especially in ER/PR-positive and HER2-negative tumors while its benefits are less pronounced in the triple-negative breast cancer subgroup. This aligns with previous research, such as the SEER data analysis, which demonstrated that prognostic staging significantly alters survival predictions. By integrating molecular biomarkers, prognostic staging offers a more personalized approach to treatment, optimizing therapeutic interventions and improving outcomes for LABC. As survival rates continue to improve, the need for precise prognosis prediction becomes critical for effective treatment planning. Integrating advanced tools, such as radio-genomics, may further enhance prognostic accuracy, helping to refine personalized care in breast cancer management.

## REFERENCES


1. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 72: 409-436, 2022.
2. Tabár L, Duffy SW, Vitak B, et al. The natural history of breast carcinoma: what have we learned from screening? Cancer 86: 449-462, 1999.
3. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353: 1784-1792, 2005.
4. Aebi S, Karlsson P, Wapnir IL. Locally advanced breast cancer. Breast 62 Suppl 1(Suppl 1): S58-s62, 2022.
5. Specht J, Gralow JR. Neoadjuvant chemotherapy for locally advanced breast cancer. Semin Radiat Oncol 19: 222-228, 2009.
6. Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr (30): 96-102, 2001.
7. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 15: 2483-2493, 1997.
8. Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 22: 4691-4699, 2004.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17: 1471-1474, 2010.

10. Tran WT, Childs C, Probst H, et al. Imaging Biomarkers for Precision Medicine in Locally Advanced Breast Cancer. J Med Imaging Radiat Sci 49: 342-351, 2018.

11. Park YH, Lee SJ, Cho EY, et al. Clinical relevance of TNM staging system according to breast cancer subtypes. Ann Oncol 22: 1554-1560, 2011.

12. Loibl S, Poortmans P, Morrow M, et al. Breast cancer. Lancet 397: 1750-1769, 2021.

13. Harbeck N, Gnant M. Breast cancer. Lancet 389: 1134-1150, 2017.

14. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol 37: 423-438, 2019.

15. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353: 1659-1672, 2005.

16. Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med 353: 1652-1654, 2005.

17. Jackisch C, Lammers P, Jacobs I. Evolving landscape of human epidermal growth factor receptor 2-positive breast cancer treatment and the future of biosimilars. Breast 32: 199-216, 2017.

18. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nature Reviews Drug Discovery 22: 101-126, 2023.

19. Bianchini G, De Angelis C, Licata L, et al. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol 19: 91-113, 2022.

20. Chavez-MacGregor M, Mittendorf EA, Clarke CA, et al. Incorporating Tumor Characteristics to the American Joint Committee on Cancer Breast Cancer Staging System. Oncologist. 2017;22(11):1292-300.

21. Yi M, Mittendorf EA, Cormier JN, et al. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer staging system. J Clin Oncol 29: 4654-4661, 2011.

22. Bagaria SP, Ray PS, Sim MS, et al. Personalizing breast cancer staging by the inclusion of ER, PR, and HER2. JAMA Surg 149: 125-129, 2014.

23. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol 25: 1783-1785, 2018.

24. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer. Journal of Clinical Oncology 28: 2784-2795, 2010.

25. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. Journal of Clinical Oncology 31: 3997-4013, 2013.

26. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Annals of Oncology 24: 2206-2223, 2013.

27. Tryfonidis K, Senkus E, Cardoso MJ, et al. Management of locally advanced breast cancer-perspectives and future directions. Nat Rev Clin Oncol 12: 147-162, 2015.

28. Low JA, Berman AW, Steinberg SM, et al. Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. J Clin Oncol 22: 4067-4074, 2004.

29. Dhanushkodi M, Sridevi V, Shanta V, et al. Locally advanced breast cancer (LABC): Real-world outcome of patients from cancer institute, Chennai. JCO Glob Oncol. 2021;7:767-81.

30. Yang PD, Peng QQ, Lian WB, et al. Validation of the eighth American Joint Committee on Cancer Anatomic and Prognostic Staging System for Breast Cancer. J Surg Res 270: 539-546, 2022.

31. Wang M, Chen H, Wu K, et al. Evaluation of the prognostic stage in the 8th edition of the American Joint Committee on Cancer in locally advanced breast cancer: An analysis based on SEER 18 database. Breast 37: 56-63, 2018.

32. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation Study of the American Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer. JAMA Oncol 4: 203-209, 2018.

33. Kurundkar A, Gao X, Zhang K, et al. Comparison of AJCC Anatomic and Clinical Prognostic Stage Groups in Breast Cancer: Analysis of 3322 Cases From a Single Institution. Clin Breast Cancer 18(6): e1347-e52, 2018.

34. Zhou J, Lei J, Wang J, et al. Validation of the 8(th) edition of the American Joint Committee on Cancer Pathological Prognostic Staging for young breast cancer patients. Aging (Albany NY) 12: 7549-7560, 2020.

35. Tokunaga E, Ijichi H, Tajiri W, et al. The comparison of the anatomic stage and pathological prognostic stage according to the AJCC 8th edition for the prognosis in Japanese breast cancer patients: data from a single institution. Breast Cancer 27: 1137-1146, 2020.

36. Kim EJ, Park HS, Kim JY, et al. Assessment of the Prognostic Staging System of American Joint Committee on Cancer 8th Edition for Breast Cancer: Comparisons with the Conventional Anatomic Staging System. J Breast Cancer 23: 59-68, 2020.

37. Shao N, Xie C, Shi Y, et al. Comparison of the 7th and 8th edition of American Joint Committee on Cancer (AJCC) staging systems for breast cancer patients: a Surveillance, Epidemiology and End Results (SEER) Analysis. Cancer Manag Res 11: 1433-1442, 2019.

38. Yang SP, Zhou P, Lian CL, et al. The predictive effect of the 8th AJCC pathological prognostic staging on the benefit of postmastectomy radiotherapy in N2/N3 breast cancer. Breast Cancer (Dove Med Press) 14: 133-44, 2022.

39. Kim JY, Lim JE, Jung HH, et al. Validation of the new AJCC eighth edition of the TNM classification for breast cancer with a single-center breast cancer cohort. Breast Cancer Res Treat 171: 737-745, 2018.

40. Plichta JK, Ren Y, Thomas SM, et al. Implications for Breast Cancer Restaging Based on the 8th Edition AJCC Staging Manual. Ann Surg 271: 169-176, 2020.

41. Hu J, Fung MW, Tsang JY, et al. Improved Prognostication for the Updated AJCC Breast Cancer Pathological Prognostic Staging Varied in Higher-Stage Groups. Clin Breast Cancer 20: 253-61.e7, 2020.

42. Yin L, Duan J-J, Bian X-W, et al. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Research 22: 61, 2020.

43. Luo SP, Wu QS, Chen H, et al. Validation of the Prognostic Significance of the Prognostic Stage Group According to the Eighth Edition of American Cancer Joint Committee on Cancer Staging System in Triple-Negative Breast Cancer: An Analysis From Surveillance, Epidemiology, and End Results 18 Database. J Surg Res 247: 211-219, 2020.

44. Prat A, Pineda E, Adamo B, et al. Clinical implications of the intrinsic molecular subtypes of breast cancer. The Breast 24: S26-S35, 2015.

45. Ye J, Wang W, Xu L, et al. A retrospective prognostic evaluation analysis using the 8th edition of American Joint Committee on Cancer (AJCC) cancer staging system for luminal A breast cancer. Chin J Cancer Res 29: 351-360, 2017.

46. Xu L, Li JH, Ye JM, et al. A retrospective survival analysis of Aanatomic and prognostic stage group based on the American Joint Committee on Cancer 8th Edition Cancer Staging Manual in Luminal B Human Epidermal Growth Factor Receptor 2-negative Breast Cancer. Chin Med J (Engl) 130: 1945-1952, 2017.

47. Ding J, Jiang L, Xu Z, et al. Validation of the Prognostic Stage from the American Joint Committee on Cancer 8th Staging Manual in Luminal B-Like Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer. Cancer Manag Res 14: 719-728, 2022.

48. Joo JH, Kim SS, Son BH, et al. Evaluation of the Prognostic Stage in the 8th Edition of the American Joint Committee on Cancer in Patients with Breast Cancer and Internal Mammary Lymph Node Metastasis. Anticancer Res 38: 5357-5361, 2018.

**Correspondence:**

Dr. Yasemin SENGUN

Akdeniz Universitesi Tip Fakultesi

Radyasyon Onkolojisi Anabilim Dali

Konyaalti

ANTALYA / TURKIYE

Tel: (+90-532) 333 40 55

e-mail: yaseminsengunn@gmail.com

**ORCIDs:**

| | |
|---|---|
| Yasemin Sengun | 0000-0001-8289-1713 |
| Timur Koca | 0000-0002-7400-1837 |
| Nina Tuncel | 0000-0002-3306-1577 |
| Aylin Fidan Korcum | 0000-0003-0318-6122 |