June 26th 2018
HONG KONG BREAST CANCER FOUNDATION
ANNUAL SCIENTIFIC MEETING 2018

Summary of Session 1

American Joint Committee on Cancer (AJCC) Cancer Staging – 8th Edition Selected Highlights

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New AJCC cancer staging in breast cancer 2018

The 8th Edition of the AJCC Staging Manual – effective from 1 January 2018 – applies to invasive carcinoma and ductal carcinoma *in situ* (DCIS).[1] Along with further defining TNM staging and post-neoadjuvant therapy criteria (Table), additional major changes to the staging system include:

- The addition of biomarker data to be used alongside anatomical classification in the staging of breast cancer, including tumour grade, oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and multigene panels.[1]
- Two new staging groups have been added to reflect the use of biomarkers and multigene panels: namely Clinical Prognostic Stage and Pathological Prognostic Stage.[1]
    - **Clinical Prognostic Staging** is determined prior to any treatment and is relevant for all patients. It incorporates clinical TNM information from history, physical examination and biopsies.[1]
    - **Pathological Prognostic Staging** is relevant to patients initially treated with surgery and uses the same information as clinical staging plus multigene prognostic panels.[1]
- Removal of lobular carcinoma *in situ* (LCIS) from the staging system because there is insufficient evidence that treatment is necessary, despite acknowledgment that a pleomorphic variant has similar clinical features to DCIS.[1] Lobular carcinoma *in situ* is now considered to be a benign condition.[1] This variant shares genetic and morphological features with invasive carcinomas,[2] and patients are candidates for excision if necrosis and distention are present.[3]

Table. Major amendments to TNM and post-neoadjuvant therapy criteria[1]

Criteria change	Description
Tumour (T)	Only the largest contiguous tumour is to be used to estimate tumour volume
	Measurements are to be rounded to the nearest mm except for tumours between 1–1.5 mm, which are always rounded to 2 mm to avoid misclassification as a microinvasive carcinoma (T1mi)
	Multiple simultaneous tumours are documented using the 'm' modifier
	Satellite tumour nodules in the skin (T4b) must be separated from the primary tumour and macroscopically identified
	Inflammatory carcinoma (T4d) requires a high-grade tumour, clinical features of diffuse erythema or oedema in ≥⅓ of the breast, and evidence of rapid disease progression
Lymph nodes (N)	cN0 indicates no lymph node involvement, and cNx is only used if the nodal basin has been previously removed and examination is not possible

	Add a suffix to specify the type of sample used to confirm presence of node metastases (f, fine needle aspiration; sn, sentinel node biopsy)
	Only the largest contiguous tumour deposit is used to estimate lymph node metastases volume
Post-neoadjuvant therapy (ypT and ypN)	• Only the largest contiguous residual focus of residual tumour is used in staging. The 'm' prefix is used to record multiple foci for ypT • Describe the basis of ypT/ypN classification in the pathology report and include pre-treatment classification if possible[1]
Complete pathological response	• Defined as no visible invasive tumour and no lymphovascular tumour emboli • Categorization is not downgraded for patients with detectable metastases prior to treatment, regardless of response

ypN, post-neoadjuvant therapy pathological node categorization; ypT, post-neoadjuvant therapy pathological primary tumor categorization.

Prognostic breast cancer staging

Anatomical staging remains important in clinical settings where biomarker analysis and/or targeted therapies are not available, and for enabling comparison across studies and patient populations.[1] However, staging needs to include additional biological information whenever available to guide treatment decisions.[1] Each prognostic biomarker is scored according to the degree of receptor expression or histological or nuclear grade.[1] When combined with pathological stage, biomarkers provide greater prognostic power, with improved stratification of disease-specific survival.[1,4,5]

Multigene panels have shown promise for predicting patient outcomes,[6-8] and broad agreement has been observed across commercially available tests (eg, Oncotype Dx®, MammaPrint®, Prosigna® etc).[1,7] Currently, only the Oncotype Dx score is included in the new AJCC pathological prognostic staging criteria, and only for particular subsets of patients (those with $T_{1–2}N_0M_0$, ER+, HER2- breast cancer).[1]

The new prognostic staging groups have been validated and shown to provide more accurate stratification of disease-specific survival than anatomical staging, assuming appropriate treatment.[1,9] This may have cost-effectiveness implications for treatment.

Overview of clinical decision algorithms and multigene panels from Professor Winnie Yeo

Several clinical decision-making tools are available to assist with treatment decisions for patients with breast cancer, such as Adjuvant! Online, PREDICT[10] and CancerMath.[11] Furthermore, the European Group on Tumour Markers has endorsed not just the Oncotype Dx multigene test, but also the MammaPrint, EndoPredict and Prosigna tests, for determining prognosis of patients with ER+/HER2- disease.[12] While the majority of panellists at the St. Gallen Consensus Conference 2017 indicated that multigene tests are likely unnecessary for patients with low-grade early breast cancer and pT_{1a-b} pN_0 ER+/PR+/HER2- disease, these tests could provide useful information regarding prognosis for ER+/HER2 patients.[13]

Updates from the 2018 ASCO Annual Meeting on using multigene panels to inform treatment decisions

Dr Thomas Yau noted that the benefit of chemotherapy for patients with a midrange Oncotype Dx risk of recurrence score (ie, 11–25) is uncertain, but results from the large TAILORx study (N=6,711) have indicated no difference in invasive disease-free survival and distant relapse-free survival between patients with a midrange score receiving adjuvant chemotherapy and endocrine therapy versus endocrine therapy alone.[14] However, younger patients (<50 years of age) may receive some benefit.[1]

Summary

The 8th Edition of the AJCC cancer staging system now incorporates biomarker and multigene panel data into new clinical prognostic and pathological prognostic staging alongside traditional anatomical staging protocols, providing additional guidance on personalized treatment decisions.[1]

Case study from Dr William Foo

A 44-year-old patient presented with a left breast mass (34 mm, grade 2) and no involvement of the sentinel lymph nodes. The tumour was ER+/PR+/HER2-. Anatomical staging classified the tumour as stage IIA, which pathological prognostic staging downgraded to stage IA, indicating a good prognosis assuming appropriate treatment.[1] The patient received chemotherapy based on a high Ki-67 finding and, while Dr Foo did not rely on the EndoPredict multigene panel to determine treatment, the test placed the patient in the high-risk category and supported his decision.

Case study from Dr Janice Tsang

A 59-year-old post-menopausal woman presented with a left breast mass and underwent surgery with wide local excision where she also received a sentinel lymph node biopsy. Histopathology revealed a grade 2 1.3 cm invasive ductal carcinoma with no lymphovascular invasion, lymph node negative (SLNB 0/2) and clear margins. The tumour was ER+ (Allred 8/8)/PR+ (Allred 8/8)/HER2 IHC 2+ but FISH negative, and associated with a relatively high Ki-67 level of 30%. Both anatomical and clinical prognostic staging classified the tumour as stage IA. Multigene panel testing (Prosigna with PAM50) was conducted, indicating a luminal B cancer with high risk of recurrence (ROR) score of 78. Based on histology, biomarker and multigene panel factors, the patient was offered adjuvant chemotherapy with four cycles of docetaxel-cyclophosphamide followed by adjuvant radiotherapy and endocrine therapy. Genomic profiling facilitated individualized treatment, as chemotherapy would not normally have been considered for this patient with relatively small tumour and node negative disease.

References

1. Badve SS, et al. Part XI Breast. In: Amin MB, et al (eds.). *AJCC Cancer Staging Manual. 8th ed.* Chicago, IL: The American College of Surgeons; 2017:587–636.
2. Simpson PT, et al. *J Pathol* 2005;205:248–254.
3. Sinn HP, Kreipe H. *Breast Care* 2013;8:149–154.
4. Yi M, et al. *J Clin Oncol* 2011;29:4654–4661.
5. Mittendorf EA, et al. *Ann Surg Oncol* 2017;24:3502–3509.
6. Dowsett M, et al. *J Clin Oncol* 2013;31:2783–2790.
7. Bartlett JM, et al. *J Natl Cancer Inst* 2016;108:djw050.
8. Sparano JA, et al. *N Engl J Med* 2015;373:2005–2014.
9. Weiss A, et al. *JAMA Oncol* 2018;4:203–209.
10. Henry NL, et al. *Am Soc Clin Oncol EduBook* 2017;37:106–115.
11. Miao H, et al. *BMC Cancer* 2016;16:820.
12. Duffy MJ, et al. *Eur J Cancer* 2017;75:284–298.
13. Gnant M, et al. *Breast Care* 2017;12:102–107.
14. Sparano JA, et al. *N Engl J Med* 2018;379:111–121.