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EDITORIAL

Breast surgeons at the forefront: preserving lymph nodes for enhanced immunotherapy efficacy

Zhiqiang Shi[1]*, Qiuchen Zhao[2]*, Yongsheng Wang[1], Pengfei Qiu[1]

[1]Breast Cancer Center, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China; [2]Cancer Research UK Cambridge Centre and Department of Oncology, University of Cambridge, Cambridge, CB2 0XZ, UK

The principal breast cancer treatment approach has long been surgical removal of the primary breast lesions and regional lymph nodes, particularly the axillary lymph nodes. However, the advent of minimally invasive diagnostic techniques, such as sentinel lymph node biopsy (SLNB), has markedly diminished the extent of surgery required for regional lymph nodes. Recent studies have been aimed at avoiding axillary surgery by performing preoperative imaging diagnosis in patients with low tumor burden[1,2]. Nonetheless, for most patients with breast cancer, the excision of some (sentinel) or even all regional lymph nodes remains imperative. In the past, the goals of surgical de-escalation in the treatment of regional lymph nodes in breast cancer were improving quality of life and decreasing complications, without compromising patient outcomes or survival[3]. However, this approach overlooked the critical functions of regional lymph nodes in the anti-tumor immune response. Given the increased importance of immunotherapy in breast cancer treatment, the immune response implications should be considered in decision-making regarding the method and extent of surgery. Particularly for patients anticipated to undergo immunotherapy, might a rationale exist for surgical preservation of regional lymph nodes (completely avoiding axillary surgery) to the greatest extent feasible, in light of anti-tumor immunity?

A series of clinical trials on breast cancer immunotherapy have provided surgeons with critical insights regarding the complex roles of surgical interventions and the varied success of immunotherapy across disease stages (**Table 1**). Although breast cancer was traditionally considered an immune "cold tumor"—in comparison to cancers more responsive to immunotherapy, such as lung cancer—PD-1/PD-L1 inhibitors have markedly altered the treatment landscape for certain cancer subtypes, particularly triple negative breast cancer. The differences in clinical outcomes observed between the preoperative and postoperative phases of immunotherapy trials have highlighted the substantial effects of surgical interventions. For example, the KEYNOTE-355 and Impassion130 trials validated that the efficacy of immunotherapy in advanced triple negative breast cancer is heavily dependent on PD-L1 expression levels[4-6]. In contrast, the IMpassion131 study did not replicate the previously observed survival advantages, thus prompting questions regarding the post-surgery benefits in patients with advanced disease stages[7]. Therefore, considerable uncertainties remain regarding the application of immunotherapy in advanced stages of breast cancer, given the inconsistencies in enrolled patient populations and differences in chemotherapy regimens across studies. More importantly, a large proportion of patients undergo surgical treatment, including the removal of regional lymph nodes. In early breast cancer, PD-1 inhibitors have shown promise in the neoadjuvant setting, as evidenced by the KEYNOTE-522 study, which demonstrated significant improvements in pathological complete response and event-free survival, which were unaffected by PD-L1 expression[8,9]. However, these benefits were not uniformly observed in the early postoperative adjuvant phase. In the IMpassion 030 trial, a combination of atezolizumab and chemotherapy did not significantly enhance

*These authors contributed equally to this work.
Correspondence to: Pengfei Qiu
E-mail: qiu.pf@outlook.com
ORCID ID: https://orcid.org/0000-0001-6784-410X
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Table 1 Benefits of immunotherapy across clinical trials

		Advanced breast cancer			Early breast cancer	
					Neoadjuvant treatment	Adjuvant treatment
Trial		KEYNOTE-355	IMpassion130	IMpassion131	KEYNOTE-522	IMpassion030
Was the main endpoint achieved? (yes/no)		*PFS*: no (ITT)/yes (PD-L1+) *OS*: no (ITT)/yes (PD-L1+)	*PFS*: yes (ITT)/yes (PD-L1+) *OS*: no (ITT)/no (PD-L1+)	*PFS*: no (ITT)/no (PD-L1+) *OS*: no (ITT)/no (PD-L1+)	*pCR*: yes *EFS*: yes	*iDFS*: no
Benefits of immunotherapy	ITT	PFS 7.5 m *vs.* 5.6 m; HR = 0.82 OS 17.2 m *vs.* 15.5 m; HR = 0.89	PFS 7.2 m *vs.* 5.5 m; HR = 0.80; *P = 0.0025** OS 21.0 m *vs*. 18.7 m; HR = 0.87; *P* = 0.077	PFS 5.7 m *vs.* 5.6 m; HR = 0.86 OS 19.2 m *vs.* 22.8 m; HR = 1.12	pCR 64.8% *vs.* 51.2%; *P = 0.00055** EFS 84.5% *vs.* 76.8%*	iDFS events: 11.5% *vs.* 10.2%; HR = 1.12; *P* = 0.37
	PD-L1+	PFS 9.7 m *vs.* 5.6 m; HR = 0.65; *P = 0.0012** OS 23.0 m *vs.* 16.1 m; HR = 0.73; *P = 0.00185**	PFS 7.5 m *vs.* 5.0 m; HR = 0.62; *P* < 0.0001* OS 25.4 m *vs*. 17.9 m; HR = 0.69	PFS 6.0 m *vs.* 5.7 m; HR = 0.82 OS 22.1 m *vs*. 28.3 m; H R = 1.11	pCR 68.9% *vs.* 54.9%; *P = 0.00055**	iDFS events: 9.8% *vs.* 9.3%; HR = 1.03
	PD-L1-	PFS 6.3 m *vs.* 6.2 m; HR = 0.82 OS 16.2 m *vs.* 14.7 m; HR = 0.97	PFS 5.6 m *vs.* 5.6 m; HR = 0.95 OS 19.7 m *vs*. 19.7 m; HR = 1.05	N/A	pCR 45.3% *vs.* 30.3%; *P = 0.00055**	N/A
	De novo metastasis	PFS 9.7 m *vs.* 5.3 m; HR = 0.48*	N/A	N/A	N/A	N/A
	Metastatic, recurrent (< 12 m)	PFS 7.5 m *vs.* 7.2 m; HR = 1.00	N/A	N/A	N/A	N/A
	Metastatic, recurrent (≥ 12 m)	PFS 9.9 m *vs.* 6.6 m; HR = 0.64	N/A	N/A	N/A	N/A

PFS, progression free survival; OS, overall survival; pCR, pathological complete response; EFS, event free survival; iDFS, invasive diseases free survival; ITT intention-to-treat; *difference was statistically significant.

invasive disease-free survival (iDFS) in both the general and PD-L1 positive cohorts[10]. Notably, survival benefits of immunotherapy were observed in patients who retained their complete regional lymph nodes post-surgery, as evidenced by the KEYNOTE-355 studies in advanced stage cancers, in contrast to patients with lymph node removal[4]. Preservation of regional lymph nodes was a commonality among the patients who benefited from immunotherapy in the KEYNOTE-522 and KEYNOTE-355 studies. Specific data supporting these observations are presented in **Table 1**. These results have suggested that lymph node preservation may be crucial to immunotherapy success and that the effects of surgical interventions on treatment efficacy must therefore be reconsidered.

Dr. Matthew H. Spitzer's recent research[11], published in *Cell*, has shed light on the potential of immunotherapy to activate anti-tumor CD8+ T cells within regional lymph nodes. Their results have suggested that maintaining lymph node integrity until immunotherapy completion might amplify treatment effectiveness against solid tumors. Cutting-edge single-cell RNA sequencing alongside paired TCR sequencing revealed that CD8+ T cells in tumors and their corresponding lymph nodes in patients with head and neck squamous cell carcinoma are clonally related. Furthermore, anti-PD-L1 immune checkpoint blockade (ICB) was found to affect not only T cells but also surrounding cells, such as dendritic cells, within the lymph nodes. These findings have provided the first evidence of the critical contribution of lymph nodes to the anti-tumor immune response in humans, thus underscoring the importance of lymph node preservation in enhancing immunotherapy efficacy. Although metastatic lymph nodes might foster an immunosuppressive environment, assessing the ICB response in patients with *vs.* without surgical lymph node removal or with metastatic lymph nodes remains crucial. The premature removal of regional metastatic or healthy lymph nodes before ICB treatment might undermine the potential benefits of therapy, because naive CD8+ T cells, which are essential for a robust anti-tumor response, can be primed by dendritic cells within the lymph nodes before circulating through the blood to the tumor site. These insights support a more nuanced approach to lymph node management in the context of immunotherapy, which might potentially improve treatment paradigms.

Moreover, these findings in head and neck cancer might extend to breast cancer, in which sentinel lymph nodes (SLNs) are the primary nodes affected by tumor drainage and metastasis, and are crucial in the diagnosis and management of regional lymph node metastasis through SLNB[12]. These nodes substantially overlap with tumor draining lymph nodes (TDLNs), where the immune response against tumor antigens is initiated. TDLNs facilitate the activation and differentiation of T cells into effector and memory T cells, which are essential for targeting and eliminating tumor cells[13]. ICB effectively modulates the immune response by reviving anti-tumor T cell proliferation in TDLNs—a strategy that might be more efficient than targeting the tumor microenvironment alone. These findings underscore the potential importance of SLNs in the immune response and suggest a need for further research on the roles of SLNs in enhancing immunotherapy efficacy in breast cancer.

Traditional breast cancer surgery involves extensive removal of tumors and potentially metastatic lymph nodes, and regional lymph node status is a key prognostic indicator influencing patient staging and treatment strategies. Consequently, partial or complete regional lymphadenectomy is widely used for both diagnostic and therapeutic purposes. However, emerging research and clinical trials have highlighted the major immunological roles of regional lymph nodes, particularly TDLN and SLNs, in the anti-tumor immune response. Given this immunological perspective, a revised surgical approach might preserve regional lymph nodes, particularly in patients slated for immunotherapy, to maintain this immune response. This more conservative approach to lymph node removal would balance tumor safety against the potential benefits of lymph node preservation. However, this viewpoint warrants further investigation, particularly regarding (1) the differential immune functions of metastatic *vs.* healthy lymph nodes, given that evidence from studies such as KEYNOTE-522 has suggested that patients with lymph node metastasis may benefit more from immunotherapy; (2) the specific immunological roles of SLNs *vs.* non-SLNs; and (3) the ability of remaining lymph nodes to contribute to anti-tumor immunity post-SLNB, given the altered lymphatic drainage pathways.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Wrote the article: Zhiqiang Shi, Qiuchen Zhao.
Conceived the article: Yongsheng Wang, Pengfei Qiu.

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