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D3 or not D3 . . . that is not the question

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The appropriate extent of lymph-node dissection for gastric cancer continues to be debated. Radical lymphadenectomy did not increase long-term survival after curative gastrectomy in either the landmark Medical Research Council trial[1] or in the Dutch[2] gastric trial. Proponents of radical lymphadenectomy[1] suggested that prohibitive perioperative mortality, surgical inexperience, and design flaws in those trials[2,3] might have concealed a survival benefit for radical lymphadenectomy.

This month's issue of *The Lancet Oncology* reports a randomised controlled trial[4] of nodal dissection for patients with gastric cancer by Wu and colleagues. From 1993 to 1999, this single-institution trial randomly allocated 221 patients with advanced gastric cancer at the Taipei Veterans General Hospital, Taiwan, to curative gastrectomy and local (ie, D1) lymphadenectomy, or extended (ie, D3) lymphadenectomy.[5] At a median follow-up of 94·5 months (range 62·9–135·1) patients assigned D3 surgery had an absolute overall survival benefit of 5·9% (95% CI –7·3–19·1, log-rank p=0·041). Recurrence at 5 years favoured the D3 group by 10·3% (–3·2–23·7). Its limitations notwithstanding, to our knowledge this is the first study in which one group of experienced surgeons have assessed prospectively the absolute surgical effect of extended lymphadenectomy on survival from advanced gastric cancer.

Oncological examples in which survival is increased by a more-detailed lymph-node dissection are few and level I evidence confirming a benefit is scarce. A basic tenant of surgical oncology is that cancerous lymph nodes are indicators, not governors, of survival.[6] Acceptance of the results of any study that shows a survival benefit from removal of more lymph nodes deserves critical analysis. Radical local resections, such as total mesorectal excision for rectal cancer, might limit locoregional spread of disease, but have seldom been associated with significant increases in long-term survival.

A single-institution trial with a unimodal surgical approach to advanced gastric cancer is not generalisable,

Controversies remain over the effectiveness of radical lymphadenectomy

and does not take into account the important contribution of adjuvant treatment. Some features of the trial design and data interpretation warrant assessment.

First, the preoperative work-up was limited and unreliable: 178 (53%) of the 335 patients enrolled did not fit the predefined study criteria, 114 of whom were regarded ineligible after staging laparotomy and 64 of whom did not fit the protocol histologically after randomisation. This situation highlights the evolving importance of high-quality cross-sectional imaging and endoscopic ultrasonography for accurate staging work-up to stratify patients for entry into clinical trials. The rationale for randomisation and inclusion of the 64 patients who did not fit the protocol histologically remains unclear. Although these patients were distributed equally between groups, whether they share similar biological behaviour and risk of recurrence is unclear and could have ramifications for intention-to-treat analyses.

Second , use of overall survival as a primary endpoint, instead of disease-specific survival, is problematic because 17 (15%) of the 111 deaths in the study (15%) were not related to tumour recurrence, and the actual survival benefit between groups was small.

Third, 31 of the 64 D3 patients had positive nodes in the upper echelon nodal basins (Wu CW, personal communication). Many of these patients presumably also had positive nodes in the D1 region. D3 dissection did not result in removal of a greater number of positive nodes than D1 dissection. Therefore, how does removal of more negative nodes translate into increased survival?

Fourth, there was no increased risk of recurrence in the D1 group until 2·4 years after surgery, at which point the curves intersect and diverge favouring the D3 group. Ikeda and colleagues[7] and Wu and co-workers[8] have reported previously that most recurrences arise within 2 years of curative resection. Therefore, the late risk of recurrence in patients in the D1 group is mysterious. The article[4] omits detailed anatomic information on these late recurrences and thus we can only extrapolate from retrospective reports,[8] which show that less than half of recurrences after D1 resection involve regional or distant lymphatic basins. The issue of whether residual cancerous cells in unresected lymphatic basins should be resected or treated systemically remains unanswered.

The benefit of extended lymphadenectomy will continue to be debated. Despite the impressive effort of Wu and colleagues,[4] we remain skeptical that extended lymphadenectomy directly increases survival. A significant result statistically does not always translate into a clinically meaningful benefit. The study[4] shows that the morbidity of extended lymphadenectomy, although not lethal, is substantial even in experienced hands.[9] With improvements in both neoadjuvant and adjuvant cytotoxic chemotherapy,[10,11] treatment paradigms are shifting. Although extended lymphadenectomy might improve the staging accuracy in patients with advanced gastric cancer, increased long-term survival probably needs further understanding of the biological behaviour of these tumours and the rational application of molecular technologies to overcome their ability to elude our scalpels.

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