

How does extended lymphadenectomy influence practical care for patients with gastric cancer?

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A recent study showed no benefit from extending lymphadenectomy beyond D1+ in gastric cancer. Adequate lymphadenectomy at high-volume institutions is essential for locoregional control and survival in this group of patients.

Summary

The recurrence and survival rates in patients with curable gastric cancer remain suboptimal. Debate on the optimal extent of lymphadenectomy for the surgical treatment of these patients is, therefore, still ongoing. A randomised, controlled trial by Sasako et al. (**D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer**. *N Engl J Med* 359:453–462) examined whether addition of para-aortic nodal dissection to D2 lymphadenectomy improves survival in patients with gastric cancer. The results from this trial, whose primary endpoint was overall survival, demonstrated no additional benefit of lymphadenectomy beyond D2 resection. Management strategies should focus on optimal lymphadenectomy in high-volume hospitals, with evaluation of chemotherapy and radiotherapy, to achieve low surgery-related morbidity and mortality, optimal locoregional control and improved survival rates for patients with curable gastric cancer.



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The extent of lymphadenectomy required to achieve locoregional control in gastric cancer has been debated for over two decades, and the discussion is still ongoing. Radical lymphadenectomy did not increase long-term survival after curative surgery in either the Dutch Gastric Cancer Group (DGCG) trial¹ or in the Medical Research Council (MRC) trial.² Wu et al. demonstrated improved survival for patients with gastric cancer treated with curative resection in a single-institution randomised trial after D3 lymphadenectomy compared with D1 lymphadenectomy.³ In this study, however, D3 dissection did not result in removal of a greater number of positive nodes than D1 dissection did. The choice of

overall survival as the primary endpoint in this study was questionable because 15% of deaths were not tumour-related, which reduced the observed difference between the groups in disease-specific survival.³

The study by Sasako et al. is one of the most recent to address the issue of the extent of lymphadenectomy in gastric cancer.⁴ This trial was designed to detect an overall five-year survival benefit of 8%, and 523 patients (maximum age 75 years) with stage T2b, T3 or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (D2; *n*=263) or D2 lymphadenectomy together with para-aortic nodal dissection (D2–PAND; *n*=260). The inclusion period was approximately

six years with 24 participating centres in Japan. The primary endpoint of the study was overall survival and the secondary endpoints were recurrence-free survival, surgery-related complications and hospital death. Rates of surgery-related complications in the D2-only and D2-PAND groups were 20.9% and 28.1%, respectively ($P=0.07$). Mortality from any cause within 30 days after surgery was 0.8% in both groups. In the group assigned to D2-PAND, the median operative time was 63 minutes longer and the median blood loss was 230 ml greater than in the D2-only group. The five-year overall survival rates were 69.2% and 70.3% in the D2-only and D2-PAND groups, respectively. For patients treated with D2-PAND, the hazard ratio for death was 1.03 ($P=0.85$). No significant differences in recurrence patterns or recurrence-free survival were observed in the two groups. Two-thirds of the patients ($n=348$) had positive nodes, but only 8.5% ($n=22$) had positive para-aortic nodes, which is a small number to address the question of whether D2-PAND results in better survival compared with D2 alone. No significant difference was apparent in the number of positive nodes in the two treatment groups. D2-PAND did not improve the overall five-year survival of patients with positive para-aortic nodes. The overall survival of node-positive patients ($n=348$) was better in the D2-only group (65.2%) than in the D2-PAND group (54.9%, $P=0.04$), although the overall survival of node-negative patients ($n=174$) was better in the D2-PAND group (96.8%) compared with the D2-only group (78.4%; $P=0.009$), which we think is a surprising finding.

The authors conclude that D2 plus PAND does not improve survival of

patients with curable gastric cancer, and that D2 lymphadenectomy should be performed in high-volume institutions with sufficient experience in this procedure and its postoperative management. Even though the operative mortality and overall five-year survival rates reported by Sasako et al. are impressive, the strict inclusion criteria make the results of this study not directly translatable to the general population. The authors criticise the DGCG and MRC trials because of the surgeons' limited experience of extended lymphadenectomy procedures, and the suboptimal capability of the hospitals to manage major surgical complications owing to their low numbers of cases. These trials, however, reflect what is achieved in terms of survival in the general population, better than Sasako et al.'s study. Regardless of variation in nodal dissections, no significant difference in overall survival between D1 or D2 surgery was observed in the DGCG and MRC trials.^{1,2} An autopsy-based analysis of patterns of failure with respect to the Maruyama index (MI) of 441 deaths that occurred in the DGCG trial demonstrated that isolated regional failure (8% in those with MI <5 vs 21% in those with MI \geq 5) and combined regional and distant failure (19% for the MI <5 group vs 36% for the MI \geq 5 group) occurred less frequently in the MI <5 group ($P<0.001$).⁵

MacDonald et al. assessed the effect of surgery plus adjuvant chemotherapy and radiotherapy on survival of patients with resectable gastric cancer.⁶ Only 10% of the patients had the recommended D2 lymphadenectomy and 54% had a D0 lymphadenectomy; three-year survival in the combined therapy and surgery-only groups was 50% and 41%, respectively ($P=0.005$). In the surgery-

only group, 64% of patients had relapses versus 43% of patients in the combination-therapy group ($P<0.001$).⁶ The authors concluded that postoperative chemotherapy and radiotherapy significantly improves overall and relapse-free survival, and should be considered for all patients at high risk for recurrence after curative resection, such as patients who have had D0 or D1 lymphadenectomy.⁶

Sasako et al. demonstrate that lymphadenectomy beyond D2 does not improve locoregional control.⁴ Radical surgery seems to have reached the limit of its benefit. Unfortunately, increased morbidity and mortality associated with D2 lymphadenectomy highlight that this is still a high-risk procedure. Gastric cancer treatment in high-volume institutions should focus on implementing high-quality care (i.e. in anaesthesia, surgical technique, nurse staffing and training). Low-volume institutions should monitor the completeness of resection, adequacy of lymph-node examination and their participation in clinical trials to reduce the risks of postoperative morbidity and mortality associated with gastric cancer surgery, and to improve locoregional control and survival.⁷ Other key issues that still need to be addressed are whether patients with a low MI will derive a survival benefit and improved locoregional control from chemotherapy and radiotherapy combined with surgery and optimal lymphadenectomy (i.e. ≥ 15 lymph nodes removed) without splenectomy. These issues are currently being addressed in the Dutch CRITICS randomised trial, the results of which are anticipated in eight years.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine