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Extended (D2) Lymph Node Dissection for Gastric Cancer: Do Patients Benefit?

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The optimal extent of lymph node dissection for gastric cancer has not yet been determined. There has been worldwide debate in the last two decades about the value of extended lymph node dissection. The topic has become more controversial after the very recent publication of the randomized Dutch[1] and MRC[2] trials that concluded not using extended lymph node dissection. The criticism of the Dutch trial, published in an editorial in the same issue of the *New England Journal of Medicine* as the trial itself,[3] and the contrary results from not only a specialized institution but also from an ongoing, well designed and conducted randomized control trial,[4] suggest the difficulties in drawing definitive conclusions. A critical evaluation of all theoretical, surgical-oncological principles, and clinicopathologic data available is thus necessary, in an attempt to clarify the complicated problem of the impact of extended lymph node dissection on survival.

The Japanese Research Society for the Study of Gastric Cancer (JRSGC) has standardized lymph node dissection and pathological evaluation for gastric cancer.[5] The guidelines of JRSGC recognize 16 different lymph node compartments (stations), numbered 1 through 16, that surround the stomach. These 16 nodal stations are grouped into five categories (N0 to N4). The extent of lymphadenectomy is classified according to the level of lymph node dissection (D1 to D4). The D1 procedure includes the dissection of perigastric nodes directly attached to the stomach (lymph nodes along the lesser and the greater curvature, stations 1 to 6, N1 level). In D2 procedures, the extraperigastric lymph nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), splenic artery, and splenic hilus (stations 11, 10) [N2 level] also are dissected. D3 and D4 resections include, in addition, the dissection of nodal stations 12 through 14 (N3 level), and 15 and 16 (N4 level), respectively.

The rationale for extended lymph node dissection is to clear the metastatic extraperigastric nodes that are left behind after a D1 node dissection, thus achieving better local control of the disease and survival. The JRSGC, on the basis of observational studies that showed better survival,[6] has consistently recommended extended (D2) lymph node dissection for the treatment of gastric cancer. In Japan, a Western-type limited (D1) node dissection is considered an insufficient procedure. However, the concept of extended node dissection, despite the increasing worldwide interest, is still controversial in the West. To clarify this question, two major multicenter European randomized trials that compared D1 with D2 dissection were conducted and another, an Italian trial, is ongoing. The conduct of such a trial in Japan, the country that introduced the concept of extended node dissection, and now presents the best treatment results world wide, is considered unethical. In the Dutch and MRC trials, with 711 and 400 patients, respectively, patients underwent randomly assigned treatment with curative intent. Both trials found that the rates of short-term morbidity and hospital mortality (10% vs. 4% and 13% vs. 6%, respectively) were substantially higher among the patients who had D2 dissection. In both trials, the analysis of long-term survival showed that there were no long-term improvements in survival or decrease in the risk of relapse among patients who had a D2 dissection.[1,2] For these reasons, the authors of these trials do not recommend extended lymph node dissection for Western patients.

What reasonable conclusions can we draw from both randomized trials? Should these results be considered conclusive, even though they are contrary to those from observational studies, so there is no longer any indication for D2 dissection for Western gastric cancer patients?

The problem is extremely complicated. According to the recent movement of "evidence-based medicine,"[7] randomized control trials (RCTs) are the best methods for evaluation of the effectiveness and appropriateness of

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treatments. In practice, especially in surgery, there are limitations of RCT.[8] Numerous variables, as analyzed below, confound the comparison of D1 and D2 procedures in both endpoints of these trials: the short-term outcome and the long-term survival.

The main argument, and at the same time, the main disadvantage, of both trials is the finding that D2 dissection increases short-term morbidity and in-hospital mortality. However, this adverse effect was attributable largely to the resection of the spleen and the tail of the pancreas in the D2 group, as well as the participation of surgeons who were less familiar with the D2 dissection technique because they did only one or two D2 procedures per year.[3] The short-term results of these trials contrast with those results from institutions with experienced surgeons who have performed D2 dissections.[9] In-hospital mortality after D2 dissection is now reported to be very low, $<1\%$ nation-wide in Japan and $<2\%$ in specialized Western centers.[10] Interestingly, these results are now confirmed in the ongoing Italian study of more than 318 randomized patients; the well designed trial includes a pancreas-preserving technique for the D2 procedure.[4] These results establish that D2 dissection, performed by experienced surgeons and with a spleen and pancreas preservation, can be performed with the same safety as a D1 procedure. Professor Brennan, in his editorial on the Dutch trial, points out that the patient can only be harmed by an extended lymph node dissection when it is performed by an inexperienced surgeon.[3]

Whereas the effect of D2 dissection on short-term outcome is now clear, its beneficial effect on long-term survival is still controversial. Conflicting results are found in the available long-term survival data. Impressive high stage (II, IIIA)-specific survival rates have been shown after D2 dissection in many observational studies,[6,9] but it has been reported that these are attributable largely to stage migration.[11] This phenomenon, that D2 dissection provides more lymph nodes for examination and refines pathological staging, increases stage-specific survival in D2 groups without a real survival improvement. The best way to eliminate stage migration is by comparing long-term survival among all patients who had a D1 or D2 dissection with curative intent. At present, there has been no study that could show an overall survival benefit.

Similarly inconclusive are the results of both randomized trials. D2 node dissection did not improve long-term survival or decrease the risk of relapse, but the D1 and D2 groups were not well balanced. Resection of the spleen and pancreas was independently associated with reduced long-term survival, but splenectomy and pancreatectomy was performed significantly more often in D2 than in D1 groups ($P < 0.05$).[1,2] Furthermore, despite the great efforts of the authors for standardization and quality control, major non-compliance was noted in 51% of D2 patients as indicated by an incomplete node dissection at the intended level.[1] Multi-center cooperation allows sufficient accrual, but has the disadvantage of introducing surgeons without technical ability in the conduct of D2 node dissection. This may result in an incomplete nodal dissection (non-compliance) with residual metastatic N2 nodes that may be the source of fatal relapse and reduced survival for D2 patients.

The pitfalls of the randomized trials on both endpoints, short-term outcome and long-term survival, and the difficulties for protocol adherence of such a challenging surgical trial, underline the problems for the interpretation of these results as conclusive.

The need to evaluate the effectiveness of extended lymph node dissection, while avoiding a conventional comparison between D1 and D2 groups with the disadvantages of stage migration, noncompliance, compliance (lymph node removal outside of the intended level of dissection) and other related variables, caused the development of a new method for evaluation and was recently published.[10] The advantage of D2 versus D1 node dissection is the clearance of extraperigastric N2 lymph nodes. The metastatic N2 nodes that are left behind after a D1 dissection are the source of subsequent fatal relapse. Consequently, the evaluation of clinicopathologic data and long-term outcome of patients with metastatic N2 nodes (N2 disease), who had undergone a D2 node dissection with curative intent, can help prove whether this procedure is of benefit.[12] The hypothesis that was tested was: "Patients with N2 disease but without apparent distant metastasis (TanyN2M0), have at surgery a localized disease so that a D2 node dissection results in both R0-resection and cure in some of these patients." The hypothesis is confirmed only when the survival analysis shows that there are long-term survivors among these N2 patients. In this case, the therapeutic benefit of D2 node dissection will be as great as the proportion of possible N2 long-term survivors.[10]

A standardized protocol was developed and designed especially based on this concept. All clinicopathologic and follow-up data were prospectively carefully documented. Our results showed that among all patients who had a D2 dissection with curative intent, 25% had positive extraperigastric N2 nodes. Among patients with node-positive disease, one of two also had positive extraperigastric level 2 nodes.[13] This result is a critical point for the need of D2 node dissection in order to achieve a R0 resection and is confirmed by an earlier report of the Dutch trial[11] and by recent Japanese stud-

ies.[14] These pathohistological data establish the Japanese experience: that the risk of residual disease in N2 nodes and fatal relapse among the patients with node-positive disease undergoing D1 dissection with apparently curative intent, is very high, about 50%.[11,13,14] The relapse-free survival rate at 5 years in our study was 20%, and the overall survival rate was 17% among N2 patients who had a D2 node dissection with curative potential.[10,13] This result confirms the tested hypothesis and reflects the survival benefit of D2 dissection. However, this therapeutic benefit, when calculated for all patients who had resections with curative intent, in our study was small, about 5%. Similar low results were calculated by Siewert et al.[9] for the survival benefit of D2 resection. This finding may explain why all prospective control trials have failed to demonstrate any significant difference in overall survival for D2 patients because more than 1000 R0 patients would have to be randomized to detect such a marginal change in the overall prognosis with a power of 90% at a significance level of 0.05.[9] Because the subgroup of N2 patients in our study was small ($n = 31$) and the reported 5-year survival rate from Japanese specialized centers for these patients was 2-fold greater, about 39%,[14] there is a need for a major prospective study based of our concept to clarify which patients, and in what proportion, among those with N2 disease benefited from extended lymph node dissection.

D2 node dissection with a systematic and standardized pancreas-preserving technique is as safe as a D1 procedure. This has been confirmed by the Italian ongoing randomized trial. Furthermore, when the histopathological data from the Dutch trial are evaluated according to our method, they will confirm the results of our study and the Japanese studies that reported the risk for treatment failure when a D1 node dissection is supplied is substantially high. For patients with node-positive disease, D1 dissection results in residual extraperigastric N2 nodes and fatal relapse in 50% of patients. A curative resection for these patients is achievable only with a D2 node dissection that has resulted in disease-free survival at 5 years, as in 20% of our patients. Thus, taking into account that at present, there is no proven effective adjuvant treatment, D2 node dissection, as the only treatment modality affording a chance of cure in some N2 patients, is the treatment of choice, at least for patients with node-positive disease.

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