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SPECIAL ARTICLE

Proof-of-Concept Changes Treatment Guidelines for Gastric Cancer

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ABSTRACT

Treatment of gastric cancer has been controversial. Studies on extent of surgery have showed conflicting results and evidence from randomized controlled trials (RCTs) is insufficient to support treatment guidelines. Currently, a proof[1] of the concept[2] that extensive D2 node dissection results in cure a substantial proportion of N2 patients, who have no chance of cure with D1 dissection, has been demonstrated. However, D2 increases operative mortality in inexperienced hands and is not superior to D1 dissection for patients with N0 or N1 disease [Japanese anatomical nodal classification system].[3] These findings partially explain the failure of RCTs available to demonstrate a significant *overall* survival benefit. Is the emerging evidence sufficient for recommendations on surgical treatment of gastric cancer?

Surgery is the standard of care for gastric cancer with principal goal, whenever feasible, the complete resection of the tumor, a so-called R0 resection.[4] However, the extent of lymph node dissection in a R0 resection has been a hot topic of debate for several decades. Despite surprising results in nonrandomized studies from Japan and specialized Western institutions, improved survival after extensive D2 versus limited D1 dissection has not yet been demonstrated in RCTs.

Less extensive surgery consisting of gastrectomy, partial or total depended on the tumor location and stage, with limited D0/D1 lymph node dissection has been the routine clinical practice in the treatment of patients with gastric cancer in the USA[5,6] and Europe.[7] But credible evidence indicates that D0/D1 dissection is associated with residual nodal disease in patients with advanced N2 positive nodes.[7] Overall 5-year survival rate is only 23% in the USA[8] probably as a result of surgical undertreatment, even according to US authors themselves.[5] The corresponding rate with a D2/D3 dissection as the standard procedure in Japan is over 60%.[9] Can this difference be explained, at least partially, by the different extent of lymphadenectomy in these two countries?

The controversy on D2 over D1 dissection is not surprising if we consider the multiple factors that confound the assessment of the impact of these dissections on long-term survival.[7] These factors include hospital and surgeon volume and their effect on postoperative in-hospital mortality and completeness of D2 dissection,[10-12] the so-called Will Rogers or stage migration phenomenon,[13] which cannot be avoided even in RCTs,[7,10-12] and magnitude of absolute survival benefit expected and sample size needed to detect a significant difference.[10-12]

To eliminate all these factors and bias, a new concept was published in 1998.[2] The idea was simple but rational. The gain of D2 over D1 dissection is the additional removal of the extraperigastric N2 nodes around the celiac axis. An expected survival benefit by D2 dissection should therefore be focused on patients with N2 positive nodes and not to those with N0 or N1 stage of disease who can be equally effectively treated with D1 dissection. The therapeutic index of D2 dissection is equal with the cure rate, if there is, of N2 patients after D2 dissection. In a prospectively defined protocol, 125 patients were identified to have undergone a curative D2 dissection, on the basis of a quality control of all clinical, surgical, and pathohistological findings.

Of these 125 D2, R0 patients, 31 had a pN2 nodal stage of disease. In a prespecified subgroup analysis, survival rate in the pN2 subgroup of patients was 20% at 5 years[2] and 10 years.[14] Our estimates, under the hypothesis that all these N2 patients die after a D1 "R0" resection because of residual positive N2 nodes, suggest

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that this is the survival benefit of D2 over D1 dissection. Now, 6 years later, the proof of this concept by the final results of the Dutch RCT[1] may reverse the current status in the surgical treatment of gastric cancer. Of 711 patients who had undergone an R0 resection in the Dutch trial, N2 nodal involvement had 50 of 380 D1 patients and 47 of 331 D2 patients. Eleven years after resection, there was no survivor among the 50 D1 patients in contrast to a **cure rate of 21%** among the 47 D2 patients.[1]

These data completely confirm both of our hypotheses: (a) None patient with N2 disease can be cured by D1 dissection and (b) the therapeutic index of D2 dissection in N2 patients is substantial, at least 20%. This fact is clinically very important because D2 dissection is currently the single treatment available able to provide cure in a considerable proportion of N2 patients.

Overall survival was not significantly better after D2 dissection in the Dutch trial. This is not a surprising finding. In their report, Hartgrink et al.[1] conclude that the increased postoperative mortality in D2 group offsets its long-term effect. Considering this finding as well as that the benefit of D2 dissection is restricted to N2 patients only and not to those with N0/N1 disease, it is clear that a much larger sample size with adequate number of N2 patients in D1 and D2 groups would be required in the Dutch trial to have the power to detect a significant difference in overall survival.

Among N2 patients, who are experienced the greatest benefits by D2 dissection? Emerging evidence from a RCT[15] and retrospective studies[9,14] consistently indicates that these are patients with a serosa-negative disease. Indeed, patients with serosa-negative gastric cancer face a low risk of developing peritoneal or distant recurrence. Therefore, D2 dissection resulting in an effective local and regional nodal control, leads to high survival rates.[9,14-16] By stark contrast, even the most perfectly and completely performed extended lymph node dissection has major limitations if both serosa and N2 nodes are positive. Recent data suggest very high recurrence rates and poor survival even after a curative D2/D3 node dissection.[9,14] Because of these limitations of D2/D3 surgery alone, RCTs (MAGIC, EORTC, Swiss trials) are underway to assess whether extensive node dissection combined with perioperative adjuvant treatment could improve survival. However, at the moment no data are available. The encouraging results of the Intergroup study (INT-0116)[6] involving chemoradiotherapy after surgery, which has been suggested as the standard of care in the USA, unfortunately have no implication in patients undergoing D2 dissection. In this study, although D2 dissection was advised, it was performed in only 10% of patients. The survival benefit observed with adjuvant treatment may compensate the inadequate surgery. Survival results with D2 surgery alone appear to be superior to those with D0/D1 resection plus adjuvant chemoradiation.[1,2,9,17]

Targeted lymph node dissection is undoubtedly the ideal treatment. Patients receive the adequate surgery and surgical complications by unnecessary lymphadenectomy are avoided. But this goal at the moment is unrealistic. Even with the most modern imaging or other approaches, nodal status cannot accurately be predicted before or even during surgery. Therefore, all patients with potentially curable disease, including those with N0 or N1 disease, should undergone D2 dissection. In this case, what is the absolute overall survival benefit expected by D2 dissection? As this rate is depended on the incidence and survival of N2 subgroup of patients, our estimates suggest that the absolute overall survival benefit ranges between 2.95% (14% incidence x 21% survival) in the Dutch trial[1] to 6% (30% N2 incidence x 20% survival) in our own study[2,14] and 8% (20% x 40%) in Japanese reports.[9]

The debate on the safety of D2 dissection has definitively been ended. More recent RCTs,[15,18,19] in contrast to previous RCTs,[1,20] provide convincing evidence that D2 node dissection without pancreatico-splenectomy performed by high-volume surgeons, is a safe procedure. In-hospital mortality in these trials is lower than 1%.[15,18,19]

Extended lymphadenectomy has been recommended by the Japanese Society for Research in Gastric Cancer, the European Society of Surgical Oncology, the International Gastric Cancer Association, and the US National Comprehensive Cancer Network. Experts with the largest experience in lymphadenectomy around the world, as Brennan,[21] Siewert,[22] Sano,[23] and Sasako,[9] also recommend this procedure for experienced surgeons. The current proof-of-concept adds strong evidence for the safety and effectiveness of D2 dissection performed by high-volume surgeons. The emerging evidence is now sufficient to guidelines for a wider clinical use of D2 procedure. The low incidence of D2 dissection outsides Japan, can and should be increased by training surgical residents and fellows in the technique of extended lymphadenectomy. D2 dissection however, is a dangerous procedure in inexperienced hands[21] and should be avoided by low-volume surgeons.[24]

Future

Toward individualized lymphadenectomy, recent data with sentinel node biopsy (SNB)[25] and genomic[26] approaches promise accurate prediction of nodal status which will allow a guide lymph node dissection. However, much more research work and long time is needed for validation by RCTs and translation of research into personalized clinical practice.

For most patients with non-early-stages cancer survival can be improved if systemic therapy be combined with adequate D2 surgery to eliminate free cancer cells and micrometastatic disease. But despite efforts no conclusive data for gastric cancer are available. However, the multimodality therapy concept has successfully been tested in RCTs in other solid tumors such as breast cancer, colorectal and lung cancer. These data provide hope that complete surgical resection and perioperative adjuvant treatment, particularly with newer chemotherapeutic agents as cisplatin and taxanes in polychemotherapy-based regimens, and radiotherapy will

significantly improve survival also for patients with gastric cancer.

The greatest and rational expectations for improved cancer therapy, arise from increasing understanding of the human genome and advances in molecular biotechnology. A revolution has already been started and promises to transform clinical practice from empirical treatment to a predictive, individualized targeted therapy. Discovery-based research aimed at molecular abnormalities involved in the pathogenesis, growing and metastasis of cancer, while sparing normal cells, will lead to personalized highly-effective treatment of cancer. The list of targeted agents approved by the U.S. Food and Drug Administration is steadily growing. This list includes monoclonal antibodies (HER2, trastuzumab [Herceptin]), for the treatment of breast cancer, and small molecules inhibitors (tyrosine kinases receptors are ideal targets) for the treatment of lung cancer (gefitinib [Iressa]), and colorectal cancer (Cetuximab, Erbitux; Bevacizumab, Avastin).[26] Many other novel drugs will be developed that are targeted to a signalling molecule. Ultimately, because of the plasticity of the cancer-cell genome, it will be essential to develop combination therapies involving small-molecule and antibody cocktails that function through distinct and complementary mechanisms of action in order to achieve the rapid and complete eradication of tumours.[26] There is hope that such novel agents will also be developed for the multimodality treatment of gastric cancer. Adequate surgery and adjuvant treatment in effective combinations with chemotherapy, radiotherapy, and targeted molecular therapy will improve both survival and quality of life of patients with gastric cancer.

However, at the moment and until credible evidence provides proof for the safety and effectiveness of such novel personalized therapy, extended lymph node dissection should become the standard of care for most patients with potentially curable disease. Intensive training of surgeons is required for a safe rise of D2 dissection incidence in the Western world. This strategy undoubtedly will increase the curability rate including patients with N2 positive nodes, who have no chance of cure by any other treatment modality currently available. Furthermore, D2 dissection should be the basis of research aimed at developing combined empirical and targeted therapies, because it increases the effectiveness of adjuvant perioperative treatment through minimizing residual disease.

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