controversial topics in surgery

Radical D2 gastrectomy for cancer

How extensive should a gastrectomy be for treatment of gastric cancer? D2 resections are not frequently undertaken in the UK following two randomised controlled trials of D1 versus D2 gastrectomy. These showed increased mortality and morbidity following D2 resections (with little survival increase in uncomplicated cases) largely as a result of the effects of pancreatic and splenic resections in the D2 cases.

Sue-Ling, an exponent of D2 resections, points out the methodological flaws of the trials, including poor surgical quality control. He argues that gastric cancer metastasise firstly to lymph nodes, thus supporting the case for extended lymphadenectomy. Khan and Mason hold a contrary view: they

demonstrate the stage migration effect of wider lymphadenectomy and highlight the absence of evidence for better long-term survival between D1 and D2 resections.

Many UK surgeons adopt a compromise D1.5-type gastrectomy, *i.e.* extended lymphadenectomy, omentectomy but with preservation of the spleen and pancreas. This compromise operation might be more suited to the UK patient whose stage at presentation is invariably more advanced than witnessed in Japan.

Tom Dehn

E: thomas.dehn@rbbh-tr.nhs.uk

The case for D2 resections

HENRY M SUE-LING

Department of Surgery, Leeds General Infirmary, Leeds, UK

CORRESPONDENCE TO:

Henry M Sue-Ling, Department of Surgery, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK

E: henry.sue-ling@leedsth.nhs.uk

Judged by the standards of colon, breast and rectal surgery for cancer, the operation as commonly practiced for gastric cancer is wholly inadequate.

Appleby LH. *Cancer* 1953; **6**: 704–7

These prophetic words were uttered over 50 years ago by a Western surgeon from Canada, LH Appleby, who went on to describe the Appleby technique of left upper quadrantectomy for cancer. In his seminal paper on the block dissection of lymph nodes around the coeliac axis for gastric cancer, Appleby also suggested that: 'If improvement in the results of surgery for cancer of the stomach is to be brought about, a much wider and more thorough removal of the drainage area of the stomach must be encompassed than has hitherto been thought possible'. Yet, despite the fact that Appleby and other surgeons in the West recognised the need for more radical surgery for gastric cancer many years ago, it was largely the

Japanese who brought home the concept of radical resection for gastric cancer to Western surgeons. Based on their meticulous investigation of the pathological spread of gastric cancer to regional lymph nodes, they showed through numerous studies^{1,2} that extended lymph node dissection produced improvements in the survival of patients with gastric cancer. Admittedly, the vast majority of these studies, until recently, have been retrospective and, therefore, subject to bias. Nevertheless, the sheer volume of these studies, the large number of patients and the enormous attention to detail have been impressive.

D2 lymph node dissection

The level of lymph node resection is denoted by the prefix D: D1 is removal of N1 nodes, D2 removal of N2 nodes, D3 removal of N3 nodes and so on (Figs 1 and 2). This should

Figure 1 Lymph node groups 1–6 (N1)

not be confused with the extent of gastric resection which depends largely on the site of the tumour in the stomach: a sub-total gastrectomy is performed for tumours of the antrum or distal stomach and a total gastrectomy for tumours of the middle or proximal stomach. A standard D2 resection for gastric cancer involves removing not just part or the whole stomach, but also the N1 (groups 1–6) and N2

Figure 2 Lymph node groups 7–11 (N2)

(groups 7–11) lymph nodes, the greater and lesser omenta and if necessary, the spleen and tail of the pancreas for tumours of the proximal stomach in order to remove groups 10 and 11 lymph nodes (Figs 1 and 2).

Pathological basis for D2 dissection

Critics of this operation argue that an extended lymph node dissection is not logical and does not alter the behaviour or biology of this type of cancer. Indeed, they often cite the more conservative approach to breast cancer and question whether a radical D2 resection for gastric cancer is as logical as a Halsted mastectomy for breast cancer. However, the behaviour of these two types of cancer differ in a number of important respects. Gastric cancer has a great propensity to spread through the rich plexus of lymphatics of the stomach to local or regional lymph nodes. Lymph node involvement for T1 tumours (mucosa) is 10%, T1 tumours (sub-mucosa) 20%, T2 tumours (muscle) 50% and T3 tumours (serosa) 70%. Yet, despite this great propensity to spread to local lymph nodes, gastric cancer, unlike breast cancer, remains for a long time as a locoregional disease and only in its very advanced stages is there spread via the blood stream to other organs such as the liver, lungs or bones. It is striking too, that when gastric cancer recurs it often does so locoregionally rather than more wide-spread dissemination.⁵

Gastric cancer is, therefore, a disease which, *par excellence*, is amenable to cure by the classical surgical methods of resection of the stomach, the greater and lesser omenta and N1 and N2 lymph nodes as suggested by Appleby and others over 50 years ago and popularised by our Japanese colleagues. Support for this assertion can also be found in the survival figures for these two types of cancer. It is very rare for gastric cancer to recur 5 years after surgery, whereas for breast cancer, disseminated micrometastases continue to take their toll some 10–20 years after surgery.

Application to Western patients

In Japan, the standard operation for gastric cancer is a radical D2 resection, with a reported mortality of 1% or less and overall 5-year survival figures of 60–70% in most centres. However, impressive though these figures may be, the improvements in outcome are not just down to radical surgical techniques. Gastric cancer is diagnosed at a much earlier pathological stage than it is in the West, with upwards of 50% of patients in some centres being diagnosed with early gastric cancer through a mass screening programme. Because of this, there has been a trend in Japan towards more physiological and less radical

surgery in such patients. Endomucosal resection (EMR) is performed in patients with small T1 tumours confined to the mucosa where there is very little risk of lymph node involvement. There is also an increase in the use of laparoscopic resection with sentinel node mapping for early gastric cancer invading through to the sub-mucosa where the risk of lymph node involvement is higher. However, it must be emphasised that such 'tailored' surgery is only applicable to patients with early gastric cancer (T1 tumours) which is seldom seen in the West. More advanced (T2–T4) tumours are still treated by radical surgery with extended D2 lymph node dissection.

The introduction of the D2 gastrectomy to the West has met with limited success and created a great deal of controversy. Two large scale, randomised trials of D1 versus D2 gastrectomy for gastric cancer were set up in Britain⁴ and in The Netherlands.⁵ Both studies showed that mortality and morbidity were significantly higher in the group that underwent D2 resection compared to that of the D1 group and there was no evidence of an improvement in survival in the D2 group. A number of important lessons have been learnt from both of these trials. It is now widely accepted that these trials were introduced too hastily and the surgeons who took part had very little experience of doing a D2 gastrectomy.⁶ Indeed, for such a complex operation as a D2 gastrectomy, there is a steep learning curve. It is estimated that a surgeon needs to do approximately 30–40 of these operations before becoming proficient at this procedure.⁷ It is, therefore, not surprising that there was such a considerable mortality in the D2 group of some 10–15% and any potential survival benefit of the D2 operation was probably lost in these high mortality figures. Most of the increase in morbidity and mortality in the D2 group was thought to be related to the resection of the spleen and pancreas and preservation of these two organs has been advocated by a number of authors.^{8,9} Indeed, recent randomised trials of D2 gastrectomy with or without splenectomy have shown no benefit from removing the spleen.¹⁰ It is also interesting to note that in the British MRC trial,⁴ the patients who did best were those who underwent a D2 resection with preservation of spleen and pancreas.

The more recent randomised trials of D1 versus D2 resection in Italy¹¹ and Taiwan¹² have shown that the D2 resection can be done safely in specialist centres with a mortality of 0–3% and a significant improvement in survival in patients who undergo D2 resection.¹² Other specialist centres from the West have also reported encouraging results in non-randomised trials. The German multicentre trial¹⁵ showed that mortality was similar in patients who underwent a D2 resection compared to those who had a D1 procedure (5% in each group). The study from Leeds¹⁴ also

showed that survival after D2 gastrectomy, on a stage-for-stage basis, was similar to that reported from Japan.

Conclusions

The operation of a D2 gastrectomy for gastric cancer remains a controversial subject. There is, however, increasing evidence that this operation can be done safely in the West with acceptable mortality and good survival figures. It is undoubtedly a complex operation with a steep learning curve. To achieve the best results, D2 gastrectomy should be done by experienced surgeons operating out of specialist units in the West.

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The case against D2 resections

AAMIR Z KHAN, ROBERT C MASON

Department of Surgery, Guy's and St Thomas's Hospitals, London, UK

CORRESPONDENCE TO

Aamir Z Khan, Specialist Surgical Registrar, Department of Surgery, 1st Floor North Wing, St Thomas's Hospital, Lambeth Palace Road, London SE1 7EH, UK. E: aamirzkhan@yahoo.com

Surgical resection remains the only treatment that offers patients with gastric cancer a chance of cure or long-term survival. Radical surgery (D2) including removal of the second tier of lymph nodes with *en bloc* resection of the spleen and tail of pancreas has been proposed as the operation of choice in Japan and it seems apparent that results of gastric cancer surgery there are superior to those obtained in the West. However, before comparing the results of D2 gastrectomy with less radical surgery, it would be prudent to look at some confounding factors that may have important bearing on interpretation of data.

One of the main reasons for advocating radical lymphadenectomy is that lymph node metastases are the commonest mode of spread in gastric cancer and, in theory, spread progressively along the 'tiers' described in previous section Figures 1 and 2. However, detailed pathological analysis shows that lymph node involvement is not always progressive along these tiers due to the abundant intramural network within the gastric wall.¹ Therefore, in planning radical lymphadenectomy, consideration must be given to the likelihood of metastases in the lymph node group, the proposed survival benefit of the lymphadenectomy and risks posed to the patient in terms of morbidity and mortality.

Stage migration and limitation of Japanese data

The Japanese Research Society for Gastric Cancer has standardised criteria for lymph node dissection and pathological examination after gastrectomy with more detailed analysis than is practiced in the West leading to more accurate staging.² Rather than extended lymphadenectomy, this is responsible for improved stage-specific survival and is termed the 'stage migration' effect.³ Examination of figures from the National Cancer Center in Tokyo clearly show the impact progressive tiers of lymph node involvement may have in terms of survival with a 20% survival benefit for N1 versus N2 involvement for the same T stage.⁴ Impressive high-stage (II, IIIA)-specific survival rates have been shown after D2 dissection in many observational studies but it has been reported that these are attributable largely to stage migration.⁵ 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.

The evidence from Japan is based on large observational studies spanning many years from specialist centres. There are no randomised studies from Japan supporting D2 over less radical operations and recommendations are based after comparing results to historical controls. In a country like Japan where these radical operations are performed with very low mortality rates (<1%), it is considered unethical to conduct a randomised control trial with a 'less-er operation'. However, the uptake of these operations has been slow in the West mainly due to higher morbidity and mortality attached to the extended resections.

Results of randomized trials

According to the recent movement of 'evidence-based medicine', randomised controlled trials are the best method for evaluation of the effectiveness and appropriateness of treatments. 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% versus 4% and 13% versus 6%, respectively) were substantially higher among the patients who had D2 dissection and appeared to be related to resection of the tail of the pancreas and removal of the spleen.^{6,7} In both trials, 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. For these reasons, the authors of these trials did not recommend extended lymph node dissection for Western patients. Admittedly, the trial from the Chinese University of Hong Kong compared D1 with D3 gastrectomy but again found no survival advantage in the radical surgery group; however, a higher complication rate, greater transfusion requirement and longer hospital stay were encountered.⁸ Similar conclusions were reached in the Cape Town trial which analysed outcomes at 5.1 years.⁹

Long-term outcome of patients with isolated N2 disease who have a D2 lymphadenectomy needs to be evaluated more transparently. Future trials must be designed to test the hypothesis that patients with primary tumours of any size and localised nodal disease within the second tier have long-term survivors. If so, then this is the small subgroup of patients that would stand to benefit from an extended lymphadenectomy

in direct proportion to the number of such patients in the study. However, data support the fact that, by the time patients have involvement of the second tier of nodes, one in two patients will already have lymph node involvement beyond the second tier. The difficulty will be to identify this group of patients pre-operatively.

Conclusions

There is no evidence to support the routine use of D2 gastrectomy for the surgical treatment of cancer of the stomach. Both the MRC and the Dutch trials failed to show any benefit but had higher complication rates particularly related to resection of the spleen and the tail of the pancreas. The results from observational studies that show an improved, stage-specific outcome without overall benefit for stages II and III are largely attributable to 'stage migration' rather than extended lymphadenectomy.

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