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META-ANALYSIS OF D1 VERSUS D2 GASTRECTOMY FOR GASTRIC ADENOCARCINOMA

Manjunath S Subramanya
Department of Surgery, Mount Isa Base Hospital, Mount Isa, Queensland, Australia
E-mail: manjunathbss9@yahoo.com

Md Belal Hossain
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments, University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: bjoardar2003@yahoo.com

Shahjahan Khan
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments, University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: khans@usq.edu.au

Breda Memon
Ipswich Hospital, Chelmsford Avenue, Ipswich, Queensland, Australia
E-mail: bmemon@yahoo.com

Muhammed Ashraf Memon
Ipswich Hospital, Chelmsford Avenue, Ipswich, Queensland, Australia
Mayne Medical School, School of Medicine, University of Queensland, Brisbane, Queensland, Australia
Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
Faculty of Health Science, Bolton University, Bolton, Lancashire, UK
E-mail: mmemon@yahoo.com

ABSTRACT

Objectives: To conduct a meta-analysis of randomized controlled trials evaluating the relative merits of limited (D1) versus extended lymphadenectomy (D2) for proven gastric adenocarcinoma.

Data Sources and Review Methods: A search of Cochrane, Medline, PubMed, Embase, Science Citation Index and Current Contents electronic databases identified randomized controlled trials published in the English language between 1980 and 2008 comparing the outcomes D1 vs D2 gastrectomy for gastric adenocarcinoma. The meta-analysis was prepared in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement. The six outcome variables analysed included length of hospital stay; overall complication rate; anastomotic leak rate; re- operation rate; 30 day mortality rate and 5 year survival rate. Random effects meta-analyses were performed using odds ratios and weighted mean differences.

Results: Six trials totalling 1876 patients (D1=946, D2=930) were analyzed. In five out of the six outcomes the summary point estimates favoured D1 over D2 group with a statistically significant reduction of (i) 7.12 days reduction in hospital stay (WMD -7.12, CI -12.90, -1.35,

p=0.0001); (ii) 58% reduction in relative odds of developing postoperative complications (OR 0.42, CI 0.24, 0.71, *p*=0.0014); (iii) 59% reduction in anastomotic breakdown (OR 0.41, CI 0.26, 0.65, *p*=0.0002); 67% reduction in re-operation rate (OR 0.33, CI 0.15, 0.72, *p*=0.006) and 42% reduction in 30 day mortality rate (OR 0.58, CI 0.4, 0.85, *p*=0.0052). Lastly there was no significant difference in the 5 year survival (OR 0.97, CI 0.78, 1.20, *p*=0.76) between D1 and D2 gastrectomy patients.

Conclusions: Based on this meta-analysis, D1 gastrectomy is associated with significant fewer anastomotic leaks, postoperative complication rate, reoperation rate, decreased length of hospital stay and 30 day mortality rate. Lastly the five year survival in D1 gastrectomy patients was similar to the D2 cohort.

Keywords: D1 gastrectomy; D2 gastrectomy; Gastric Cancer; Lymphadenectomy; Meta-analysis; Randomized controlled trials; Patient's outcome; Postoperative complications

1. INTRODUCTION

Gastric adenocarcinoma is a locoregional disease with a high propensity for nodal metastasis. Therefore nodal status remains one of the most critical independent predictor of patient survival following gastrectomy for this disease (Seto et al., 1997, Siewert et al., 1998). Studies have shown that lymph node involvement occurs in 3%-5% of cases when the cancer is limited to the mucosa; 11%-25% of cases for those limited to the submucosa; 50% for T2 cancers and 83% for T3 cancers (Onate-ocana et al., 2000, De Gara et al., 2003). D1 gastrectomy entails removing lymph nodes adjacent to the stomach where as a D2 dissection extends this resection to include the nodes around the branches of the celiac axis. Therefore for T2 and T3 tumors, D1 dissection leads to non-curative intervention in the majority of patients leading to poor patient outcome. Despite these facts, the relative merits of gastrectomy with limited (D1) versus extended lymphadenectomy (D2) as an oncological treatment of gastric adenocarcinoma remains contentious. Surgeons from the west have conventionally preferred the D1 approach because (a) of lower incidence of gastric cancer and therefore fewer opportunities even in large tertiary referral centres to perform more radical forms of gastrectomy; (b) of lack of training in performing D2 resection compared to their Japanese counterpart; (c) it is technically demanding with unproven benefits based on a number of randomized controlled trials (RCTs)published to date; and (d) fear of increased risk of complications (Edwards et al., 2004). Even then, the western surgeons have achieved a 5-year survival rate of 10-30% (Degiuli m et al) with D1 resection. On the other hand surgeons in Japan (and east) have traditionally preferred the D2 approach achieving an impressive 5-year survival of 50-60% with a low morbidity and mortality (Soga et al., 1979, Maruyama et al., 1987). However, the greatest criticism of these reports from Japan demonstrating such an impressive benefit and modest morbidity and mortality from D2 resection has been the retrospective nature of the data. Nonetheless this debate has lead some researchers to address this issue objectively in the form of well designed RCTs (Degiuli et al., 2004, Dent et al., 1988, Robertson et al., 1994, Bonenkamp et al., 1995, Cuschieri et al., 1999, Wu et al., 2006) . The "issue of extended lymphadenectomy" in these RCTs has produced some conflicting results further polarizing the literature on this subject. Therefore this present meta-analysis has been undertaken to develop a better understanding of the risks and benefits of D1 and D2 procedures for the treatment of gastric cancer by pooling data from all of the available RCTs.

2. METHODS

All RCTs of any size that compared D1 gastrectomy with D2 gastrectomy for the treatment of gastric adenocarcinoma and which were published in full peer-reviewed journals in the English language between January 1980 and the end of May 2008, were considered for inclusion (Table 1). Only those studies which have reported on at least one clinically relevant outcome were included. Unpublished RCTs, non-randomized prospective and retrospective comparative trials and abstracts of RCTs presented at national and international meetings were excluded. Furthermore, studies which reported on gastric cancers other than adenocarcinoma such as lymphomas were excluded because of different biological behaviour and treatment options for these tumours.

The six outcome variables analysed included (a) length of hospital stay; (b) overall complication rate; (c) anastomotic leak rate; (d) re- operation rate; (e) 30 day mortality rate and (f) 5 year survival rate. These outcomes were thought to be important because they exert influence over practical aspects of surgical practice and policy decisions within institutions.

Trials were identified by conducting a comprehensive search of Medline, Embase, Science Citation Index, Current Contents and Pub Med databases, using medical subject headings "D1 gastrectomy", "D2 gastrectomy", "gastric cancer", "comparative study", "prospective studies", "randomised or randomized controlled trials", "random allocation" and "clinical trial". Manual search of the bibliographies of relevant papers was also carried out to identify trials for possible inclusion. Data extraction and critical appraisal were carried out by three authors (MSS, BM and MAM) for compliance with inclusion criteria and methodological quality. Standardised data extraction forms (Moher et al., 1999) were used by authors to independently and blindly summarise all the data available in the RCTs meeting the inclusion criteria. The authors were not blinded to the source of the document or authorship for the purpose of data extraction. The data were compared and discrepancies were addressed with discussion until consensus was achieved.

Evaluation of the methodological quality of identified studies was conducted using the Jadad scoring system (Jadad et al., 1996) in which each study was assigned a score of between zero (lowest quality) and 5 (highest quality) based on reporting of randomization, blinding, and withdrawals occurring within the study (Table 2).

3. STATISTICAL ANALYSIS

Meta-analyses were performed using odds ratios (ORs) and relative risk (RR) for binary outcomes and weighted mean differences (WMDs) for continuous outcome measures. A slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed values in the calculation of the original OR (Liu et al., 1996). Random effects models, developed by using the inverse variance weighted method approach were used to combine the data (Sutton et al., 2000). Heterogeneity among studies was assessed using the Q statistic proposed by Cochran (Sutton et al., 2000, Wermuth et al., 1979, Hedges et al., 1985) and I^2 index introduced by Higgins and Thompson (Higgins et al., 2002, Huedo-Medina et al., 2006). If the observed value of Q is larger than the critical value at a given significant level, in this case 0.05, we conclude that the outcome variable is statistically significant. For the computations of the confidence intervals estimates of mean and standard deviation are required. However, some of the published clinical trials did not report the mean and standard deviation, but rather reported the size of the trial, the median and range. From these available statistics, estimates of the mean and standard deviation were obtained using formulas proposed by Hozo (Hozo et al., 2005). Funnel plots were synthesized in order to determine the presence of publication bias in the meta-analysis. Both total sample size and precision (1/standard error) were plotted against the

treatment effects (OR for the dichotomous variables: complications, anastomotic leak, reoperation and mortality (Sutton et al., 2000, Egger et al., 1997, Tang et al., 2000). All estimates were obtained using computer programs written in R (R: A language and environment for statistical computing [computer program]. Version 2.8.0. Vienna: Foundation for Statistical computing; 2008). All plots were obtained using the 'rmeta' package (Lumley, The rmeta Package Version 2.14: http://cran.rproject.org/web/packages/rmeta/index.html0.

In the case of tests of hypotheses, the paper reports *p*-values for different study variables. In general, the effect is considered to be statistically significant if the p-value is small. If one uses a 5% significance level then the effect is significant only if the associated p-value is less than or equal to 5%.

4. RESULTS

There was almost a perfect agreement (κ=0.99) between the three authors (MSS, BM, MAM) regarding the inclusion and exclusion of various randomized controlled trials. Based on this agreement, a total of 6 randomized prospective clinical trials (Europe =3, Asia =2, Africa=1) (Degiuli et al., 2004, Dent et al., 1988, Robertson et al., 1994, Bonenkamp et al., 1995, Cuschieri et al., 1999, Wu et al., 2006) that included 1876 gastrectomies (D1=946 and D2=930) were considered suitable for meta-analysis (Table 1).

None of the six trials achieved a modified Jadad score of more than 2 (Table 2).

In five out of the six outcomes the summary point estimates favoured D1 over D2 group with a statistically significant reduction of (i) 7.12 days reduction in hospital stay (WMD -7.12, CI -12.90, -1.35, *p*=0.0001); (ii) 58% reduction in relative odds of developing postoperative complications (OR 0.42, CI 0.24, 0.71, *p*=0.0014); (iii) 59% reduction in anastomotic breakdown (OR 0.41, CI 0.26, 0.65, *p*=0.0002); 67% reduction in re-operation rate (OR 0.33, CI 0.15, 0.72, *p*=0.006) and 42% reduction in 30 day mortality rate (OR 0.58, CI 0.4, 0.85, *p*=0.0052). Lastly there was no significant difference in the 5 year survival (OR 0.97, CI 0.78, 1.20, *p*=0.76) between D1 and D2 gastrectomy patients (Table 3).

5. DISCUSSION

Gastric adenocarcinoma survival is proportional to the level of lymph node metastases in nodal echelons N1-N4 based on the nodal classification by the JRSGC. Surgeons in the east have routinely practiced D2 gastrectomies involving extended lymphadenectomy which provides both diagnostic and therapeutic advantage (Soga et al., 1979, Maruyama et al., 1987). However surgeons in the west have struggled to achieve similar outcome with D2 gastrectomies compared with their eastern counterparts except on occasion (Edwards et al., 2004, Lewis et al., 2002, Diaz et al., 2008, Sue-Ling et al., 1993, Pacelli et al., 1993, Siewert et al., 1993).

A number of RCTs (Degiuli et al., 2004, Dent et al., 1988, Robertson et al., 1994, Bonenkamp et al., 1995, Cuschieri et al., 1999, Wu et al., 2006) have been undertaken to investigate the issues of risks and benefits of limited vs extended lymphadenectomy. Confounding factors including patient population and their selection, operative techniques especially level of lymph node dissection, experience of the operating surgeons especially in D2 resection and outcome descriptors have fuelled the ongoing debate despite reasonable attempts being made by the authors to provide trials of high quality. The authors of this paper have undertaken a meta-analytical review based on the available RCTs data in an attempt to provide some clarification. To date D2 gastrectomy has shown better results than D1 gastrectomy in mainly retrospective studies (Pacelli et al., 1993, Siewert et al., 1993, Mansfield et al., 2004, Volpe et al., 1995). However, this has not been seen in two of the largest RCTs published in

Europe (Bonenkamp et al., 1995, Cuschieri et al., 1999). In the Dutch trial with a median follow-up of 11 year, survival rates were 30% for D1 and 35% for D2 group. The risk of relapse was 70% for D1 and 65% for D2 group. The only group which seemed to benefit was the N2 disease cohort. The 11 year survival was 0% in D1 group whereas it was 20% for D2 group (Hartgrink et al., 2004). However there is a serious concern regarding the Dutch RCT for non-compliance or contamination in the extent of lymphadenectomy performed in the two randomized arms (Bunt et al., 1994).

Five of the 6 studies reported length of hospital stay. Of these 4 had significantly longer stay for D2 group compared to D1 group. The reasons for the longer stay in D2 cohort could be multiple and include (a) prolong and more complex surgical procedures; and (b) more peri-operative complications. A protracted operating time exposes the patient to a longer duration of anaesthesia, and a greater risk of thermic, thromboembolic, cardiac and respiratory complications.

Five of the 6 trials reported data on complications. Complications ranged from simple wound infection, intra-abdominal abscess formation to anastomotic leak. Different studies have enumerated complications on different bases which made summation of the results difficult. Most of the studies have reported complication under 2 major headings, surgical and non surgical. Among the surgical complications, intra-abdominal or subphrenic abscess formation was not only commonly seen but also required reoperation in the majority of cases. The intra-abdominal sepsis was also responsible for other complications such as secondary haemorrhages and death (Robertson et al., 1994). This complication was seen exclusive in D2 group. Amongst the non-surgical complications, the pulmonary infections predominate in both the groups. The overall complication rates were significantly higher in D2 group compared to D1 cohort.

Three of the 6 trials reported an anastomotic leak rate. In all the studies the D2 group had a higher leak rate. The overall pooled data similarly showed that it was statistically significant for the D2 group. The UK (Cuschieri et al., 1999) and the Dutch (Bonenkamp et al., 1995) trials, have not specified the site(s) of the leak or timing of the leaks. In the Hong Kong study (Robertson et al., 1994). 3 anastomotic leaks were recorded, all in the D2 group at the oesophagojejunal junction (i.e following a total gastrectomy) which were treated conservatively with total parenteral nutrition with favourable outcome.

Four of the 6 trials have documented a re-operation rate. The result was statistically significant. The most common cause reported for re-operation was a sub-phrenic abscess, although the causes ranged from haemorrhage to anastomotic leaks and from retro-colic hernia to intra abdominal abscesses.

Five of the 6 trials reported on the 30 day mortality rate. Pooled data shows higher mortality rates in the D2 group, although Taiwanese and Italian studies have reported lower mortality rates in the D2 group (Degiuli et al., 2004, Wu et al., 2006). The overall result was statistically significant for D2 cohort. The factors which may be responsible for higher morbidity and mortality include (a) surgical experience in performing gastric resection (high vs low volume centre); (b) the previous gastric surgery experience; (c) the pancreatic or splenic resection. Pancreatosplenectomy recommended as part of the D2 gastrectomy in the second edition of Japanese classification (Japanese Gastric Cancer Association Japanese Classification of Gastric Carcinoma - 2nd English Edition (1998). *Gastric Cancer*. 1(1):10-24, Aiko and Sasako, 1998) [27, 48]was followed by some and not by others (Degiuli et al., 2004, Dent et al., 1988, Robertson et al., 1994, Bonenkamp et al., 1995, Cuschieri et al., 1999, Wu et al., 2006). While surgeons in the Hong Kong and Taiwanese (Robertson et al., 1994, Wu et al., 2006) studies performed pancreatic and splenic resection routinely, the rest of the surgeons except Italians, performed the resection only when the upper 2/3 of the stomach was involved (Dent et al., 1988, Bonenkamp et al., 1995, Cuschieri et al., 1999). The Italians resected the pancreas or the spleen only when the

cancer had extended into these organs (Degiuli et al., 2004). The most important outcome that all the surgeons look forward to in any cancer treatment is the 5 year survival rate. Interestingly this meta-analysis does not show any difference in the 5 year survival between the D1 and D2 group which casts doubt on the benefit of the extended gastrectomy.

6. CONCLUSIONS

D1 gastrectomy is associated with significantly fewer post-operative complications including anastomotic leaks, lower re-operation rate , decreased length of hospital stay and decreased 30 day mortality rate. Most importantly there is no difference in 5 year survival rate between the two groups. It is therefore difficult to justify the routine use of D2 gastrectomy as the standard for the management of gastric carcinoma especially when the morbidity and mortality remains high.

APPENDIX

Table 1: Details of all the RCTs

Authors	Year/Country	Type of Study	Number of Patients	
			D1	D2
Dent et al	1988/ South Africa	RCT	22	21
Robertson et al	1994/ Hong Kong	RCT	25	29
Bonenkamp et al	1995/ Netherlands	RCT	513	483
Cuschieri et al	1999/ UK	RCT	200	200
Degiuli et al	2004/ Italy	RCT	76	86
Chew-Wun Wu et al	2006/ Taiwan	RCT	110	111
Total			**946**	**930**

Table 2: Jadad's Score

Authors	Year/Country	Jadad's Score	Random-ization	Blinding	Withdrawal
Dent et al	1988/ South Africa	2	2	0	0
Robertson et al	1994/ Hong Kong	2	2	0	0
Bonenkamp et al	1995/ Netherlands	2	2	0	0
Cuschieri et al	1999/ UK	2	2	0	0
Degiuli et al	2004/ Italy	2	2	0	0
Chew-Wun Wu et al	2006/ Taiwan	2	2	0	0

Table 3: Summary of pooled data comparing D1 vs D2 gastrectomy

Outcome Variables	Pooled OR or WMD (95% CI)	Test for overall effect		Test for heterogeneity		
		Z	p-value	Q	p-value	I-squared index
Length of hospital stay	-7.12 (-12.90, -1.35)	-2.4177	0.0156	36.04	0.0001	88.9%
Overall complication rate	0.42 (0.24, 0.71)	-3.2009	0.0014	11.5	0.0215	65.2%
Anastomotic leak rate	0.41 (0.26, 0.65)	-3.7644	0.0002	0.8	0.939	0%
Re-operation rate	0.33 (0.15, 0.72)	-2.7485	0.006	3.52	0.3179	14.8%
30 day mortality rate	0.58 (0.4, 0.85)	-2.7928	0.0052	1.78	0.7753	0%
5 year survival rate	0.97 (0.78, 1.20)	-0.7662	0.7662	1.67	0.797	0%

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META-ANALYSIS OF LAPAROSCOPIC POSTERIOR AND ANTERIOR FUNDOPLICATION FOR GASTRO-OESOPHAGEAL REFLUX DISEASE

Manjunath S Subramanya
Department of Surgery, Mount Isa Base Hospital, Mount Isa, Queensland, Australia
E-mail: manjunathbss9@yahoo.com

Md Belal Hossain
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments, University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: bjoardar2003@yahoo.com

Shahjahan Khan
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments, University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: khans@usq.edu.au

Breda Memon
Ipswich Hospital, Chelmsford Avenue, Ipswich, Queensland, Australia
E-mail: bmemon@yahoo.com

Muhammed Ashraf Memon
Ipswich Hospital, Chelmsford Avenue, Ipswich, Queensland, Australia
Mayne Medical School, School of Medicine, University of Queensland, Brisbane, Queensland, Australia
Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
Faculty of Health Science, Bolton University, Bolton, Lancashire, UK
E-mail: mmemon@yahoo.com

ABSTRACT

Objectives: Although laparoscopic posterior (Nissen) fundoplication (LPF) has the proven efficacy for controlling gastro-oesophgeal reflux surgically, there remain problems with postoperative dysphagia and the inability to belch or vomit. To decrease some of these postoperative complications, laparoscopic anterior fundoplication (LAF) was introduced. The aim of this study was to conduct a meta-analysis of RCTs to investigate the merits of LPF vs LAF for the treatment of gastro-oesophageal reflux disease (GORD).

Data Sources and Review Methods: A search of Medline, Embase, Science Citation Index, Current Contents, PubMed and the Cochrane Database identified all RCTs comparing different types of laparoscopic posterior and anterior fundoplications published in the English Language between 1990 and 2008. The eight variables analysed included operative time, overall complications, rate of conversion to open, re-do operative rate, dysphagia score, heartburn rate, visick grading of satisfaction and overall satisfaction.