Published in final edited form as:

J Gastrointest Surg. 2020 October ; 24(10): 2212–2218. doi:10.1007/s11605-019-04393-9.

Comparative Effectiveness of Lymphadenectomy Strategies during Curative Resection for Gastric Adenocarcinoma

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Abstract

Background—The purpose of this study was to compare the long-term effectiveness of three lymphadenectomy strategies. We hypothesized that, compared to the traditional standard (D2) lymph node dissection strategy, the less aggressive modified standard (mD2) lymphadenectomy may offer superior effectiveness due to reduced operative morbidity and comparable long-term recurrence-free survival.

Methods—A Markov decision analysis model was created to simulate five-year outcomes across three lymphadenectomy approaches for gastric cancer: limited regional (D1), traditional standard (D2), and modified standard (mD2). The primary outcome was discounted quality adjusted life-years (dQALY). Model variable estimates were derived from outcomes data and quality of life

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Category 2

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Category 3

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Disclosure Information: None of the authors have personal, financial, or other conflicts of interest to disclose.

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estimates published in Europe and Americas within the last 15 years. One-way and probabilistic sensitivity analyses were performed for clinically-relevant variables.

Results—The mD2 lymphadenectomy offered 3.03 dQALY over five years, outperforming D2 (2.62 dQALY) and D1 (2.37 dQALY). Monte Carlo simulations indicated that both mD2 and D2 lymph node dissection strategies outperformed D1 in 94.9% of simulations. Sensitivity analyses demonstrated that the mD2 approach would be less effective than D2 if the perioperative mortality rate of mD2 was greater than 6.9% (3.2% baseline).

Conclusions—Across modern series, the modified standard mD2 lymphadenectomy is an effective alternative to the traditional D2 lymphadenectomy for patients with gastric cancer. A D1 limited regional lymphadenectomy is not recommended during gastric cancer resection.

Keywords

gastric cancer; stomach neoplasms; gastrectomy; stomach/surgery; lymph node excision

INTRODUCTION

Despite a gradual decrease in incidence ¹, gastric cancer remains the fourth most common cancer worldwide, and causes more than 700,000 deaths each year ². Recent studies have focused on adjuvant and neoadjuvant strategies to maximize the durability of curative resection ³. Within these multimodal treatment protocols, gastrectomy with regional lymphadenectomy remains a principal component of treatment for gastric cancer invading beyond the submucosa ⁴. While results of lymphadenectomy have clear prognostic implications ⁵, the therapeutic role of extended lymphadenectomy in gastric cancer continues to be debated.

Outcomes for gastric cancer have historically differed substantially by region, with series from Japan and other Eastern countries reporting consistently superior survival rates than Western counterparts ⁶. Because traditional standard lymphadenectomy (D2) had been the prevailing surgical approach in Asia, a series of randomized trials in the 1990s attempted to replicate these outcomes by comparing D2 against a limited regional lymphadenectomy (D1) in Western populations ^{7–10}. Within these trials, five-year data suggested that D2 and D1 resections yielded comparable survival outcomes, leading many to abandon the more morbid D2 operation. Some have proposed that Eastern and Western gastric cancer populations represent distinct disease processes, with lymphadenectomy serving primarily a prognostic role in the West ^{11,12}. Countering these data were subsequent large retrospective studies that demonstrated associations between resected lymph node count, staging accuracy, and survival in Western populations ^{13–15}. Although D2 lymphadenectomy provides consistently higher node yield ¹⁶, more than half of patients in the United States continue to undergo D1 resections ¹⁷.

Traditionally, a D2 lymphadenectomy implied concurrent distal pancreatectomy and splenectomy to harvest nodes from levels 10 and 11d ¹⁸. Recognizing that resection of these neighboring organs was associated with increased morbidity ^{19–21}, lymphadenectomies that spare the pancreas and spleen have gained traction. Japanese Gastric Cancer Association

guidelines define the extent of D2 lymphadenectomy based on the location of the primary tumor: for cancers of the distal stomach, splenic hilar and distal pancreatic artery nodes are no longer included in a D2 lymphadenectomy²². For a subset of proximal cancers, routine splenic preservation does not appear to compromise long-term survival²³. An alternative approach is to routinely forego removal of stations 10 and 11d, adopting a modified lymphadenectomy technique that aims to excise most, but not all, level 2 nodes. Several European studies over the past 15 years have shown that this approach may offer superior long-term outcomes compared to a limited D1 resection^{24–28}.

While individual clinical trials tend to provide useful longitudinal data, they are subject to institutional confounders. Meta-analyses address this by reporting weighted averages of key outcomes, but stop short of integrating these results with quality of life measures. The incidence of gastric cancer in Western populations is far lower than that of Eastern countries. Due to this low incidence, accrual to a contemporary prospective trial assessing lymphadenectomy strategies in the West would be challenging. The objective of this study was to synthesize the existing literature on lymphadenectomy approaches for gastric cancer through a comparative effectiveness analysis. We hypothesized that, within Western populations, the modified D2 lymphadenectomy would offer superior effectiveness due to reduced operative morbidity and comparable long-term recurrence-free survival.

METHODS

Patients

For this study, we used the baseline clinical scenario of a patient with non-cancer life-expectancy greater than 5 years with resectable gastric adenocarcinoma invading beyond the superficial submucosa. The following assumptions were made: 1) the patient is an appropriate surgical candidate for radical gastrectomy and standard lymphadenectomy, 2) the patient is able to complete perioperative chemotherapy, and 3) the patient is able to comply with routine post-treatment surveillance.

Markov Model

A comparison of long-term expected utility for two or more interventions can be calculated using a Markov decision model. With this method, an experiment is simulated in which patients are allocated to alternative interventions. Following the intervention, patients transition over time between different health states in a manner dictated by the best available clinical evidence. Units of time are measured by Markov cycles (in this study, each cycle represents 3 months). The likelihood of moving from one health state to another is estimated by transition probabilities. For example, the transition probability “recurrence rate” determines the likelihood that a patient will move from the recurrence-free health state to the recurrent cancer health state over the course of one Markov cycle. Each health state is characterized by an expected utility value. All transition probabilities and utility values are derived from peer-reviewed literature. By summing the utility values of all expected disease states over a pre-determined period of follow-up, the long-term expected utility of a given intervention can be estimated.

Decision-analysis models can incorporate estimated costs of treatment to generate cost-effectiveness analyses. However, there is a paucity of society-level utility analyses related to gastric cancer; the vast majority of utility studies are based on patient-response quality of life surveys. Conversely, there are few studies that report out-of-pocket expenses for gastric cancer care. This disconnect between cost and utility structures makes a cost-effectiveness study based on patient-level utilities and Medicare-based costs invalid. Thus, the focus of this study is comparative effectiveness analysis from the patient's perspective.

Model Design

A Markov decision model was created to represent utility from the patient's perspective (Figure 1). Three interventions were compared, all of which involved gastrectomy with lymphadenectomy. While there are a variety of systemic therapy regimens for gastric cancer, the most common current practice in United States academic medical centers are driven by findings of the MAGIC and FLOT4 trials and incorporate neoadjuvant and adjuvant chemotherapy^{29,30}. Thus, to simplify comparisons, the model established that all patients would receive neoadjuvant and adjuvant chemotherapy regardless of the assigned intervention group. Following neoadjuvant treatment, hypothetical patients were allocated to one of three comparison arms: 1) limited regional lymphadenectomy (D1), 2) traditional standard lymphadenectomy (D2), and 3) modified standard lymphadenectomy sparing nodal stations 10 and 11d (mD2).

The model incorporated potential complications from surgery and simulated 5 years of follow-up as patients progress through different health states. Based on evidence-driven transition rates, the patient may eventually develop cancer recurrence, at which point definitive chemotherapy would be pursued. Because rigorous follow-up data beyond five years were not available for all three surgical treatment options tested, the Markov model was limited to five-year analysis. Model survival variables incorporated both cancer-related and cancer-unrelated mortality.

Treatment Strategies

For this study, an assumption was made that operations are performed at high-volume centers experienced in all three lymphadenectomy approaches. Extent of lymphadenectomy was defined according to Japanese Gastric Cancer Association guidelines²². A D1 resection is defined as removal of lymph node stations 1–7. A D2 (standard) lymphadenectomy is defined as removal of D1 plus stations 8a, 9, 10, 11p, 11d, and 12a. An mD2 (modified) lymphadenectomy is defined as removal of D1 plus stations 8a, 9, and 11p, and 12a. Possible outcomes following resection include no major complication, major complication, and perioperative death. Occurrence of a major complication is associated with a 3-month period of transient disutility within the model (1 Markov cycle). Following resection, patients enter a recurrence-free survival health state. The initial postoperative Markov cycle's assigned utility is further discounted due to impaired quality of life related to chemotherapy. With each passing Markov cycle, patients may remain recurrence-free, develop recurrence, or die from cancer-related or unrelated causes. Patients who develop recurrence incur utility penalties due to disease progression and salvage chemotherapy.

Model Variables

With each Markov cycle following treatment, patients may move between disease states over time. The likelihoods of these transitions are defined by event probability estimates, summarized in Table 1. Because data from Eastern and Western institutions frequently report divergent perioperative and long-term survival outcomes, a decision was made to restrict sources for variable estimates to studies originating from Western countries^{6,11,12}. Estimates for overall and recurrence-free survival were represented by time-dependent variables in order to best approximate cancer survival curves in reality. Where available, randomized clinical trials and/or large, single- and multi-institutional longitudinal observation studies were used to create these estimates. When multiple literature sources were used to create one transition variable estimate, data were weighted by sample size.

At present, there is a paucity of data on utility estimates for patients following gastrectomy for cancer that are derived from standard gamble or time trade-off methods. However, there is robust literature on quality of life survey results in this population. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is one of the most well-validated quality of life surveys for cancer³¹, and its companion site-specific module for gastric cancer (STO22) has been used to determine post-gastrectomy quality of life. We utilized results from these surveys together with a preference-based conversion metric to estimate utility for post-operative disease states³² (Table 1). Transient disutilities over one Markov cycle were assigned for postoperative recovery. Major complications were assigned an additional disutility value. All utility variables were discounted at an annual rate of 3% over the period of follow-up, thus, the primary outcome of the model was discounted, quality-adjusted life years (dQALY).

Sensitivity Analyses

Because estimates of baseline model variables carry inherent uncertainty, sensitivity analyses were conducted to test the robustness of the model's results. Sensitivity analyses also indicate the impact of each model variable on the primary outcome of dQALY. In this way, key variables that drive dQALY can be isolated for further investigation in future research. For the purpose of sensitivity analyses, recurrence-free and overall survival variables were converted to time-independent constant estimates. Each variable in the model was represented by a triangular likelihood distribution, ranging from 50% to 150% of the baseline estimate that was derived from weighted averages of published data. One-way sensitivity analyses were performed for all variables across this range. Probabilistic sensitivity analysis was also conducted, with values for each model estimate simultaneously and randomly sampled from their respective likelihood distributions. Monte Carlo simulation was performed to assess the effect of variable imprecision using 1000 re-estimated comparisons of the model results. This simulation assessed the overall effect of uncertainty on the model-derived comparison. All analyses were performed using TreeAge Pro 2017 (TreeAge Software, Inc, Williamstown, MA).

RESULTS

Over the follow-up period of 5 years after curative gastrectomy, the mD2 modified standard lymphadenectomy offered the greatest cumulative utility at 3.03 dQALY. By comparison, the D2 approach yielded 2.62 dQALY and D1 yielded 2.37 dQALY. Cumulative utility over time for each of the three surgical approaches is shown in Figure 2.

One-way sensitivity analyses were performed for all model variables, including complication rates, surgical mortality rates, and utility estimates. Results indicate that if the surgical mortality rate for mD2 exceeds 6.9% (baseline estimate 3.2%), then the D2 approach would yield greater overall utility than mD2. Similarly, if the surgical mortality rate for D2 exceeds 13.5% (baseline estimate 2%), then the D1 approach would outperform D2 in overall utility. Notably, the long-term utility of the D1 approach would not exceed that for D2 even if the perioperative mortality of D1 is 0% (baseline 4.1%). The utility outcome of each resection approach is highly sensitive to long-term overall survival (OS). In order for D1 to out-perform D2, its 5-year OS must exceed 63.6% (baseline 38.9%). In order for D2 to out-perform mD2, its 5-year OS must exceed 62.7% (baseline estimate 52.8%), or the 5-year OS of mD2 must drop below 54.6% (baseline 59.7%). Model outcomes are not sensitive to any other variables.

Probabilistic sensitivity analysis was performed using Monte Carlo simulations while sampling variable estimates at random from triangular likelihood distributions. Utility distributions for the three surgical approaches are shown in Figure 3. Across 1000 Monte Carlo simulations, both D2 and mD2 outperformed D1 in 94.9% of simulations. The mD2 strategy was superior to D2 in 61.3% of simulations.

DISCUSSION

This study synthesizes published outcomes of gastric cancer resection in Western series with post-gastrectomy utility estimates to demonstrate that the mD2 modified standard lymphadenectomy yields the greatest cumulative utility across five-year follow-up. Because gastric cancer in Western populations is relatively rare, the majority of published data have come from single-institution, non-randomized series. Two frequently-cited randomized trials performed in the West in the 1990's comparing D1 and D2 resections in Europe are the Dutch trial and the United Kingdom MRC-ST01 trial^{9,19}. Long-term outcomes from the Dutch trial indicate an association between D2 resection and locoregional recurrence-free survival when patients are followed for greater than 5 years⁷. These seminal trials were included in our survival and recurrence-free survival variable estimates. However, perioperative mortality (15%) and complication rates (30–55%) from these trials are not reflective of modern surgical outcomes. Therefore, these trials were purposefully excluded from estimates for perioperative morbidity and mortality outcomes, and their contributions to survival estimates were adjusted to reflect modern perioperative outcomes.

To date, there has not been a randomized trial comparing mD2 with either D1 or D2 approaches. Moreover, existing data on the mD2 approach, which has gained popularity in the West, frequently do not report long-term recurrence. These challenges highlight the

impracticality of relying solely on randomized trials when comparing the effectiveness of surgical approaches in gastric cancer. While Markov decision analyses cannot approximate the rigor of a randomized clinical trial and do not indicate causality, they do offer several unique advantages. Multiple sources of data can be combined and appropriately weighted to describe rare conditions, sensitivity analyses can be used to focus attention on key variables, and clinical outcomes can be synthesized with quality of life measures to establish cumulative utility. A number of recent comparative effectiveness studies have helped to address clinical equipoise in other gastrointestinal tract malignancies^{33,34}.

The mD2 lymphadenectomy has gained favor in Western institutions over the past 15 years. Much of this trend was borne out of early trials in which the D2 approach was associated with unacceptably high perioperative mortality and complication rates^{19,20}. However, subgroup analyses demonstrated that much of the operative mortality associated with D2 was associated with distal pancreatectomy and splenectomy, two techniques traditionally considered requisite for an adequate D2. More recent series selectively preserve the pancreas and spleen as long as there is no direct tumor invasion, and morbidity data have improved substantially^{26,35–38}. While never proven in a stand-alone randomized trial in Western populations, meta-analysis and retrospective data have suggested that, with acceptable perioperative morbidity, the D2 approach may offer an advantage toward disease-specific survival compared to D1^{37,39}.

With this as the backdrop, small prospective series in the West have begun to report outcomes of the modified mD2 approach, which excises higher-yield regional nodal basins but foregoes the more distant stations 10 and 11d. Thus far, long-term outcomes data with this approach are few. In our study, data contributing to perioperative outcomes were robust (N = 625 patients), but long-term survival estimates were derived from only 166 patients. Taking this into account, sensitivity analyses become paramount to determine the relative importance of these individual variables. For example, in order for D1 to surpass D2 in effectiveness, its 5-year overall survival must exceed 64%, more than 15% higher existing estimates from prospective trials. On the other hand, it is possible that long-term overall survival of patients undergoing a D2 operation—thus far reported at approximately 53%—may approximate those undergoing an mD2 (59.7%).

Not surprisingly, perioperative mortality is an important variable in determining comparative effectiveness of these surgical approaches. Modern reports indicate far lower perioperative mortality for D2 resection compared to the randomized trials of the 1990's. The likelihood that a high-volume institution would experience greater than 13.5% perioperative mortality for this operation is very low. In fact, the reported perioperative mortality rate for D2 resection in the modern era is actually lower than that for D1. This pattern is most likely a result of reporting and selection biases, as D2 resections are more likely to be performed on otherwise healthy patients at high-volume referral centers. Taking this into account, sensitivity analysis demonstrates that D1 would not outperform D2 or mD2 even with a perioperative mortality rate of 0%.

This study's results do not conclusively support a meaningful utility difference between mD2 and D2. This finding is in accord with current guidelines from the Japanese Gastric

Cancer Association, which indicate that the distal splenic artery and splenic hilum node basins may be left in situ during a D2 dissection for distal gastric cancers²². However, because the criteria necessary for D1 to outperform D2 or mD2 are not realistic, we believe that the D1 operation is less effective than the more aggressive alternatives. This reasoning is supported by probabilistic sensitivity analyses which demonstrated inferiority of D1 in nearly 95% of Monte Carlo simulations. While most high-volume centers have encouraged a more extensive lymphadenectomy strategies to improve lymph node yield and staging accuracy, many surgeons continue to perform D1 resections. A recent analysis of the Surveillance, Epidemiology, and End Results database revealed that 58% of patients have less than 15 lymph nodes removed during resections for gastric cancer—a node yield that is highly unlikely with a D2 or mD2 approach^{17,36}. Even modern series from high-volume referral centers have reported that up to half of patients do not undergo a mD2 or D2 resection⁴⁰.

Despite its conceptual appeal, a Markov decision-analysis approach has several inherent limitations. First, the data contributing to a Markov model's variable estimates are derived from a variety of institutions, patient populations, and time periods. Second, because a Markov decision analysis model is a fundamentally different approach than a direct comparative trial, measures of confidence such as p-value do not apply; instead, probabilistic sensitivity analyses can provide a broad view of the confidence of a model's outcomes. Perhaps more important than the primary outcome of the study are the results of one-way sensitivity analyses, which focus attention on the few variables that drive the model's outcomes. For example, our data demonstrate that post-gastrectomy outcomes should focus primarily on perioperative mortality for mD2 and D2, as well as long-term overall survival. Finally, because the primary outcome of this study is dQALY, analyses assume that there is a constant conversion factor between quality of life survey scores and utility. A preference-based derivation of utility from the EORTC QLQ-C30 was previously reported by Rowen and colleagues³². This formed the basis of the utility estimates used for our model. However, to our knowledge a derivation specifically focusing on the gastric cancer QLQ-C30 STO22 does not yet exist. Such a study would lend greater clarity to the utility of patients in post-gastrectomy health states.

When comparing D1, D2, and mD2 lymphadenectomies for gastric cancer, high-volume centers may choose between D2 and mD2 approaches based on provider expertise and expect comparable long-term effectiveness. Because D1 consistently under-performed compared to D2 and mD2, we do not recommend this limited approach to resection. Future reporting on surgical outcomes should focus on overall survival beyond 5 years for the mD2 approach and preference-based measures of utility after gastrectomy.

ACKNOWLEDGMENTS

This work was supported by the L30 CA220861 Award from National Cancer Institute and Grant #IRG 81-001-26 from the American Cancer Society to VMZ and by the Institutional National Research Service Award T32 CA 163177 from the National Cancer Institute to BG and KL.

Funding: This work was supported by the L30 CA220861 Award from National Cancer Institute and Grant #IRG 81-001-26 from the American Cancer Society to VMZ and by the Institutional National Research Service Award T32 CA 163177 from the National Cancer Institute to BG and KL.

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Figure 1: Markov process for management of gastric cancer with neoadjuvant chemotherapy followed by resection. “M” marks entry point of Markov process

Figure 2:
Cumulative utility for D1, D2, and modified standard (mD2) resections for gastric cancer

Figure 3: Projected utility for D1, D2, and modified standard (mD2) surgical approaches across 1000 Monte Carlo simulations. Box-and-whisker plot shows minimum, maximum, first- and third-quartiles, and median. Utility measured in discounted quality adjusted life-years (dQALY)

Table 1:

Model Variables

Variable Estimate	Baseline Value	N (total)	Sources
Surgical Mortality			
D1	0.041	1074	8,21,27,35–38
D2	0.020	1155	8,21,26,35–38
mD2	0.032	625	24–28,35
Surgical Complication			
D1	0.203	1012	8,21,27,35–38
D2	0.185	1113	8,21,26,36–38
mD2	0.197	552	24–28
Overall Survival (1, 3, 5 year)			
D1	0.84, 0.60, 0.48	1006	9,10,19,27,37
D2	0.86, 0.62, 0.53	1126	9,10,19,37
mD2	0.91, 0.66, 0.60	166	25,27
Recurrence-Free Survival (1, 3, 5 year)			
D1	0.71, 0.44, 0.32	629	8,9,19
D2	0.76, 0.51, 0.41	650	8,9,19,26
mD2	0.91, 0.57, 0.46	36	26
Utilities			
Postoperative, uncomplicated		593	32,41–43
Month 1	–0.187		
Month 2–6	–0.075		
Postoperative, complicated			
Month 1–3*	–0.253		
Month 4–6*	–0.125		
Chemotherapy	–0.2	NA	44
Disease-free survival	0.95	593	32,41–43
Disease progression	–0.12	NA	45