Are We Lacking Economic Evaluations in Gastric Cancer Treatment?

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Published online: 6 September 2014
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The rapid evolution of gastric cancer treatment in the face of escalating costs mandates thorough cost-effectiveness analyses to optimally direct future research and decision making. Relative to other cancer sites, the literature lacks high-quality economic evaluations to supplement clinical efficacy and effectiveness studies. As the fourth most commonly diagnosed cancer and the third leading cause of cancer-related death [1], gastric cancer is a major clinical and financial burden. Yet, very few estimations and assessments of overall costs of existing treatment methods or evaluations of cost effectiveness have been performed and fewer still meet current standards of high-quality

methodology. Existing reports are often far from transparent, and very few studies present their findings according to established guidelines for the reporting of health economic data [2]. Furthermore, the few studies that have examined the overall costs of a gastric cancer diagnosis and treatment have determined that it is one of the most expensive cancers to treat on a per-patient basis [3, 4]. In the last 30 years, fewer than 30 papers have been published in English attempting to assess the costs of a gastric cancer diagnosis or explicitly compare the costs and benefits of treatment alternatives. In comparison, using the MeSH heading “Costs and Cost Analysis” in MEDLINE, over 300 review articles are identified for breast cancer, over 300 review articles identified for colorectal cancer, and over 100 review articles for prostate cancer; thus indicating that enough primary literature exists to generate these numerous reviews. In addition to the scientific literature, rigorous health technology assessments for new drugs and technologies are more commonly performed by government regulatory bodies such as the National Institute for Health and Care Excellence (NICE) and published as peer-reviewed reports. Searching the NICE guidance website uncovered an additional six technology appraisals since 2004, and one intervention appraisal [5]. As a clear disparity exists for economic evaluations for gastric cancer, we do not have an evidence-based understanding of how these costs are accumulated, or a comparative ratio of costs to benefits of commonly used treatment options to guide decision making.

Few studies published in the last 20 years come from North America or Europe [3, 4, 6–9]. The majority of work evaluating the economic impact of gastric cancer and its various treatment strategies was performed in Asia, where the incidence of disease is much higher, and a larger proportion of early curative gastric cancer is diagnosed and

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treated. These differences in the presentation of gastric cancer make it difficult to project generalizations of cost and cost effectiveness from a healthcare system delivering care to a common cancer onto a system with a low incidence of disease.

Many of the existing studies are outdated as standard practice including diagnostics, the advent of new laparoscopic and robotic surgical approaches, available chemotherapeutics, and the delivery of healthcare have changed so drastically that the results of existing comparisons are both irrelevant and uninformative. Given the complexity of multidisciplinary care of gastric cancer patients [10–13], there is an opportunity to use economic evidence to help guide decision making at a policy level, where decisions about drug reimbursement are made, at the hospital or institutional level where budgetary and operational decisions are made, and at the physician level, where decisions that include a consideration of costs and benefits may aid in the reduction of unnecessary spending. Evidence exists demonstrating that costs and resource constraints should be considered explicitly in the development of policies [14]. Within the context of curative-intent treatments, two important issues must be considered for cost-effectiveness analyses: surgery and adjuvant therapies.

Surgery is the cornerstone of curative treatment for gastric cancer patients [11–13]. It is therefore not surprising that the majority of articles on the cost of treatment focused on either the operative or peri-operative costs of care. All studies assume clinical equipoise between treatment strategies and those that make statistical comparisons only do so with costs. A recent multivariate regression analysis performed by Lee et al. [15] regarding the independent determinants of the cost of gastrectomies for gastric cancer found that multiple factors increased the cost associated with the procedure, including gender, age, Charlson score, and hospital volume. Interestingly, the mean cost of a gastrectomy at a high-volume hospital was significantly lower than at a low-volume hospital (US\$2,578 vs. US\$5,011; $p < 0.001$) [15]. Clinical evidence suggests that patients who receive surgical procedures for gastric cancer at high-volume specialized centers have better short-term outcomes than those who receive their care at low-volume institutions [16]. Lee et al. provide further evidence that for an expensive to treat cancer, such as gastric cancer, with a complex surgical procedure, the referral of patients to high-volume centers may improve not only the quality of care but also may be associated with lower treatment costs [15, 16]. Whether or not this relationship would translate to different systems in a low-incidence country is unclear; however, it highlights an area worthy of future research to help inform policy.

Recently, there has been increased interest in minimally invasive resections for gastric cancer. Compared with open

surgery, where costs range from US\$2,892 to US\$30,309 (2012) depending on the extent of lymphadenectomy and type of reconstruction method [17–22], the costs of minimally invasive surgery appear to be favorable, from US\$2,091 (2012) [23] for an endoscopic mucosal resection, to upwards of US\$5,895 to US\$10,279 (2012) [17, 19, 21, 22] for a laparoscopic distal gastrectomy. Although open and laparoscopic operations have similar clinical outcomes and robotic operations are on the horizon, they have yet to be compared from a formal economic standpoint. The costs of open vs. laparoscopic gastrectomy in early gastric cancer patients have been compared; however, incomplete methodology and informal analyses preclude the use of this information in policy and decision making [17, 19, 22]. Further economic evidence is required to understand how surgical innovation impacts the costs and resource use of treating gastric cancer.

In addition to surgery, peri-operative chemotherapy [24] and adjuvant chemoradiation [25] have resulted in better patient outcomes when compared with surgery alone in randomized controlled trials. Although head-to-head comparisons do not exist to compare relative efficacy, clinical equipoise is assumed [26], and practice is driven by institutional, physician, and patient preference. The costs and resource use implications have not yet been formally incorporated into the decision-making process and we lack this information to guide policy recommendations [26]. Wang et al. conducted an economic evaluation using the data from the Intergroup 0116 randomized clinical trial [25] to compare the economic benefit of chemoradiation following surgery in comparison with surgery alone, and reported an incremental cost per quality-adjusted life-year (QALY) of US\$42,521 for adjuvant chemoradiation [9]. No formal economic evaluation for the peri-operative regimens has been performed. Provision of in-depth economic evaluations founded on clinically relevant information would support the development of an efficient and cost-effective treatment strategy.

Surgery is the foundation of curative treatment; however, the majority of gastric cancer patients in North America and Europe are diagnosed with metastatic disease, necessitating non-curative management [27, 28]. Current standard of practice for non-curative management includes a number of first- to fifth-line palliative chemotherapy agents [12, 29]. Wagner et al. [29] assessed the efficacy of chemotherapy vs. best supportive care, combination vs. single agent chemotherapy, and different combination chemotherapy regimens in advanced gastric cancer and has shown that chemotherapy significantly improves survival in comparison to best supportive care. Norum et al. [8] published the only comparison of chemotherapy regimens in the scientific literature in the last 30 years, comparing ELF (etoposide, leucovorin, 5-fluorouracil) and FAM (5-

fluorouracil, adriamycin, mitomycin C) regimens for advanced non-curative disease. They reported US\$276,153/QALY for ELF; however, this information is no longer clinically useful as it does not correspond to currently recommended treatment regimens.

Only four formal economic evaluations comparing gastric cancer treatment options were published in the scientific literature in the previous 20 years, and their results are provided in Table 1 [9, 30–32]. The shortage of formal cost-effectiveness analyses may be explained by the central role that surgery plays in treatment and the perceived diminished role of adjuvant therapy, as public and private reimbursement authorities often mandate rigorous economic evaluations to consider funding a new pharmaceutical or health technology. Of the four published in the scientific literature, two modeled the costs of using trastuzumab in addition to chemotherapy in the non-curative management of stage IV HER2+ patients alongside the trastuzumab for gastric cancer trial, and were performed from the perspective of the Japanese and Chinese healthcare systems [31, 32]. The cost per QALYs varied from US\$78,274 to US\$294,488 (2012). In the NICE review of trastuzumab for metastatic gastric cancer, they reported a base-case incremental cost-effectiveness ratio of £62,800

per QALY gained (US\$98,025) and recommended its use for subsets of patients [33]. This range of costs in relation to benefit may be prohibitively expensive in certain healthcare systems, explaining why there is a lack of universal reimbursement for trastuzumab for metastatic gastric cancer.

A number of opportunities exist to incorporate economic evaluations into the evidence base of gastric cancer treatment. Economic evaluations may be performed prospectively alongside randomized controlled trials or alternatively by combining clinical outcome data with cost data using modeling techniques. Population-based evaluations of gastric cancer care may be performed to understand the ‘real world’ impact of new chemotherapeutics, surgical techniques, or other interventions, by measuring resource use and clinical outcomes tracked in large multicenter administrative databases. It is also important to reflect that outside of Asia, the highest rates of gastric cancer occur in Eastern Europe and South America, in countries that may not have the resources or infrastructure to develop or prioritize policy based on the results of these commonly used methods of health technology assessment from North America or Europe [1]. These countries will require special consideration in how to best measure the

Table 1 Incremental cost/life-year gained and cost/quality-adjusted life-year gained (2012 US\$) as reported in the four formal economic evaluations from the literature comparing treatment regimens in the treatment of stomach cancer

References	Patient population	Intervention	Perspective	Comparator	Incremental cost/LYG*	Incremental cost/QALY*
Wang [9]	Stage 1b-IVM0	Gastrectomy + chemoradiation (INT 0116 Protocol)	Third-party payer	Gastrectomy alone	NR	\$42,521
Wu [32]	HER2+ advanced gastric cancer	Trastuzumab + chemotherapy (fluorouracil + platinum)	Chinese health care system	Chemotherapy alone (fluorouracil + platinum)	\$224,894	\$294,988
Shiroiwa [31]	HER2+ (all definitions) advanced gastric cancer	Trastuzumab + platinum-based chemotherapy	Japanese health care payer	Platinum-based chemotherapy alone	\$115,275	\$156,547
Shiroiwa [31]	HER2+ (IHC 2+/FISH+ or IHC 3+) advanced gastric cancer	Trastuzumab + platinum-based chemotherapy	Japanese health care payer	Platinum-based chemotherapy alone	\$85,389	\$118,122
Shiroiwa [31]	HER2+ (IHC 3+) advanced gastric cancer	Trastuzumab + platinum-based chemotherapy	Japanese health care payer	Platinum-based chemotherapy alone	\$55,503	\$78,274
Hultman [30]	Gastric cancer + peritoneal metastases	CRS + HIPEC + EPIC (various regimens)	NR	Chemotherapy alone (variety of regimens)	\$177,782	\$186,791

LYG life-year gained, NR not reported, QALY quality-adjusted life-year, FISH fluorescence in situ hybridization, IHC immunohistochemical, CRS cytoreductive surgery, HIPEC hyperthermic intraperitoneal chemotherapy, EPIC early postoperative intraperitoneal chemotherapy

* Costs were adjusted for inflation to the year 2012 and exchange rates to US\$ by the authors for comparison

cost effectiveness of gastric cancer treatment and implement those findings in the future.

Identifying areas of cost saving in an era of cost deficits, budget cuts, and the unnecessary use of services requires the publication of economic evaluations in tandem with the assessment of clinical benefit. The absence of high-quality economic evidence may compromise (1) new drugs being reimbursed through public and private payer systems, (2) clinicians' ability to make evidence-based decisions about the adoption of new technology or in the face of clinical equipoise, (3) the capacity for policy makers to plan for health services and technology use, and (4) our understanding of the societal impact of opportunity cost in the funding of gastric cancer treatment. How these decisions are currently being made, and how they may potentially impact clinical outcomes for gastric cancer patients is unknown. More research in gastric cancer is required to provide high-quality cost-effectiveness data to supplement what is known clinically about disease management, and will require close collaboration between health services and policy researchers, health economists, and clinicians.

Conflict of Interest Statements Alyson Mahar declares no conflicts of interest.

Abraham El-Sedfy declares no conflicts of interest.

Savtaj Brar declares no conflicts of interest.

Ana Johnson declares no conflicts of interest.

Natalie Coburn declares no conflicts of interest.

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