

Original Investigation

Processes of Care in the Multidisciplinary Treatment of Gastric Cancer

Results of a RAND/UCLA Expert Panel

Savtaj S. Brar, MD, MSc; Alyson L. Mahar, MSc; Lucy K. Helyer, MD, MSc; Carol Swallow, MD, PhD; Calvin Law, MD, MPH; Lawrence Paszat, MD, MSc; Rajini Seevaratnam, MSc; Roberta Cardoso, RN, PhD; Robin McLeod, MD; Matthew Dixon, MD; Lavanya Yohanathan, MD; Laercio G. Lourenco, MD; Alina Bocicariu, MD; Tanius Bekaii-Saab, MD; Ian Chau, MD; Neal Church, MD; Daniel Coit, MD; Christopher H. Crane, MD; Craig Earle, MD, MSc; Paul Mansfield, MD; Norman Marcon, MD; Thomas Miner, MD; Sung Hoon Noh, MD, PhD; Geoff Porter, MD, MSc; Mitchell C. Posner, MD; Vivek Prachand, MD; Takeshi Sano, MD; Cornelis van de Velde, MD, PhD; Sandra Wong, MD; Natalie G. Coburn, MD, MPH, FRCSC

IMPORTANCE There is growing interest in reducing the variations and deficiencies in the multidisciplinary management of gastric cancer.

OBJECTIVE To define optimal treatment strategies for gastric adenocarcinoma (GC).

DESIGN, SETTING, AND PARTICIPANTS RAND/UCLA Appropriateness Method involving a multidisciplinary expert panel of 16 physicians from 6 countries.

INTERVENTIONS Gastrectomy, perioperative chemotherapy, adjuvant chemoradiation, surveillance endoscopy, and best supportive care.

MAIN OUTCOMES AND MEASURES Panelists scored 416 scenarios regarding treatment scenarios for appropriateness from 1 (highly inappropriate) to 9 (highly appropriate). Median appropriateness scores from 1 to 3 were considered inappropriate; 4 to 6, uncertain; and 7 to 9, appropriate. Agreement was reached when 12 of 16 panelists scored the scenario similarly. Appropriate scenarios agreed on were subsequently scored for necessity.

RESULTS For patients with T1N0 disease, surgery alone was considered appropriate, while there was no agreement over surgery alone for patients T2N0 disease. Perioperative chemotherapy was appropriate for patients who had T1-2N2-3 or T3-4 GC without major symptoms. Adjuvant chemoradiotherapy was classified as appropriate for T1-2N1-3 or T3-4 proximal GC and necessary for T1-2N2-3 or T3-4 distal GC. There was no agreement regarding surveillance imaging and endoscopy following gastrectomy. Surveillance endoscopy was deemed to be appropriate after endoscopic resection. For patients with metastatic GC, surgical resection was considered inappropriate for those with no major symptoms, unless the disease was limited to positive cytology alone, in which case there was disagreement.

CONCLUSIONS AND RELEVANCE Patients with GC being treated with curative intent should be considered for multimodal treatment. For patients with incurable disease, surgical interventions should be considered only for the management of major bleeding or obstruction.

JAMA Surg. 2014;149(1):18-25. doi:10.1001/jamasurg.2013.3959
Published online November 13, 2013.

← Invited Commentary page 25

+ Supplemental content at
jamasurgery.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Natalie G. Coburn, MD, MPH, FRCSC, Sunnybrook Health Sciences Centre, Ste T2-60, Division of Surgical Oncology, Odette Cancer Centre, 2075 Bayview Ave, Toronto, Ontario, Canada, M4N 3M5 (natalie.coburn@sunnybrook.ca).

Gastric cancer (GC) is responsible for 10% of all cancer deaths worldwide.¹ Although surgery remains the cornerstone of curative therapy for GC, chemotherapy and chemoradiotherapy have been incorporated into treatment decisions following the publication of studies showing improved survival.²⁻⁵ Despite the evidence of a survival benefit, many patients do not receive appropriate treatment, with up to 43% eligible for multimodality treatment undergoing surgery alone.^{6,7} Survival rates for patients with GC are known to vary considerably between regions and among institutions, and these disparities may be attributable in part to the complexity of treatment decisions and differences in quality of care.

Unfortunately, many patients with GC in Western countries have metastatic disease. Prognosis is exceptionally poor for these patients.⁶ While it is generally agreed that treatment for noncurative GC should be focused primarily on palliation, retrospective series of highly selected patients suggest a potential modest survival benefit with resection.⁸ The utility of surgical treatment for metastatic GC is thus controversial, and the appropriate treatment strategy remains unclear.

The management of GC remains challenging because of the incomplete evidence and suboptimal guidance on the best care, which has been shown to lead to variation of treatment and outcomes. Since few surgeons in Western countries treat high volumes of patients with GC, lack of experience may further contribute to suboptimal care and regional variation. Defining optimal processes of care has been shown to improve clinical care for many conditions. Consequently, a rigorously derived consensus of clinical experts is invaluable to establish appropriate practice and associated performance measures to evaluate quality of care. The RAND/UCLA Appropriateness Method (RAM) is a well-described method that has been developed to help determine appropriate care for patients in situations where strong, evidence-based guidelines are not possible.⁹ The aim of this study was to organize an international panel of experts to clarify appropriate and necessary processes of care for the multidisciplinary treatment of patients with GC.

Methods

The method followed the RAM manual.⁹ The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre. Panelists were recruited through solicitation of nominations from the heads of surgical, medical, and radiation oncology units at all major cancer centers in North America, as well as corresponding authors of articles on the clinical management of GC. From the applicants, a multidisciplinary expert panel of 16 physicians from 6 different countries with expertise in the care of GC was assembled, balancing practice type and geographic location, with a focus on surgical representation (Table 1). A detailed literature review^{8,10-20} was conducted to inform the development of clinical scenarios and for reference for the panelists. Matrices of clinical scenarios regarding the multidisciplinary management of GC were written. These scenarios were pilot-tested on 3 surgical oncologists (C.S., C.L., and 1 other) and revised to a total of 416 unique scenarios, shown in Tables 2, 3, 4, 5, and 6 and eTables 1 through 6 in the Supplement.

The scenarios and literature review^{8,10-20} were sent to the panelists. For each scenario, the panelists were asked to score for appropriateness, defined as “the expected health benefit of an intervention exceeding the expected negative consequences by a wide enough margin that the procedure is worth doing, regardless of cost.”²¹ Appropriateness was scored from 1 (highly inappropriate) to 9 (highly appropriate).⁹ Panelists returned the scores and data were analyzed for areas of agreement.

The panel met in Toronto, Ontario, Canada, from October 22 through 24, 2010. Discussion was focused on areas of disagreement. Some scenarios were rewritten for clarification based on recommendations from the panelists. All scenarios were rescored for appropriateness. In the final analysis, a procedure was classified as appropriate if the median rating was 7 to 9, with agreement; inappropriate if the median rating was

Table 1. Expert Panel Members, Specialty, and Hospital Affiliation^a

Name	Specialty	Country	Affiliation
Tanios Bekaii-Saab	Medical oncology	United States	Ohio State University
Ian Chau	Medical oncology	England	Royal Marsden Hospital
Neal Church	General surgery	Canada	University of Calgary
Daniel Coit	Surgical oncology	United States	Memorial Sloan-Kettering Cancer Centre
Christopher H. Crane	Radiation oncology	United States	MD Anderson Cancer Center
Craig Earle	Medical oncology	Canada	University of Toronto
Paul Mansfield	Surgical oncology	United States	MD Anderson Cancer Center
Norman Marcon	Gastroenterologist	Canada	University of Toronto
Thomas Miner	Surgical oncology	United States	Rhode Island Hospital
Sung Hoon Noh	Surgical oncology	Korea	Yonsei University College of Medicine
Geoff Porter	Surgical oncology	Canada	Dalhousie University
Mitchell C. Posner	Surgical oncology	United States	University of Chicago
Vivek Prachand	Laparoscopic surgery	United States	University of Chicago
Takeshi Sano	Surgical oncology	Japan	Cancer Institute Hospital
Cornelis van de Velde	Surgical oncology	the Netherlands	Leiden University Medical Centre
Sandra Wong	Surgical oncology	United States	University of Michigan Health System

^a Mediator: Robin McLeod, MD, general surgery, University of Toronto, Toronto, Ontario, Canada. Panel convenor: Natalie G. Coburn, MD, MPH, surgical oncology, University of Toronto, Toronto, Ontario, Canada.

Table 2. Gastrectomy Without Preoperative Therapy^a

Stage	Proximal, No Major Symptoms	Proximal, Major Symptoms	Distal, No Major Symptoms	Distal, Major Symptoms
cT1N0	Appropriate (7.5)	Appropriate (8.0)	Necessary (8.0)	Necessary (8.0)
cT2N0	Necessary (8.0)	Necessary (8.5)	Necessary (8.0)	Necessary (8.0)
cT1-2N1	Necessary (8.5)	Necessary (8.5)	Necessary (8.0)	Necessary (8.0)
cT1-2N2-3	Appropriate (8.5)	Appropriate (8.5)	Appropriate (8.5)	Necessary (8.0)
cT3-4N0	Appropriate (8.5)	Necessary (8.0)	Appropriate (8.5)	Necessary (8.0)
cT3-4N1	Appropriate (8.5)	Appropriate (8.5)	Appropriate (8.5)	Necessary (8.0)
cT3-4N2-3	Appropriate (8.0)	Appropriate (8.0)	Indeterminate (7.5)	Appropriate (8.0)

^a Results shown as final level of agreement (median appropriateness score on a scale of 1-9) or when applicable (median necessity score on a scale of 1-9). Bold results represent agreement on score.

Table 3. Perioperative Chemotherapy^a

Stage	Proximal, No Major Symptoms	Proximal, Major Symptoms	Distal, No Major Symptoms	Distal, Major Symptoms
cT1N0	Inappropriate (1.0)	Inappropriate (1.0)	Inappropriate (1.0)	Inappropriate (1.0)
cT2N0	Indeterminate (3.0)	Indeterminate (3.0)	Indeterminate (3.0)	Indeterminate (3.0)
cT1-2N1	Indeterminate (7.0)	Indeterminate (7.0)	Indeterminate (7.0)	Indeterminate (7.0)
cT1-2N2-3	Appropriate (7.0)	Indeterminate (7.0)	Appropriate (7.0)	Indeterminate (7.0)
cT3-4N0	Appropriate (7.0)	Indeterminate (7.0)	Appropriate (7.0)	Indeterminate (7.0)
cT3-4N1	Appropriate (7.0)	Indeterminate (7.0)	Appropriate (7.0)	Indeterminate (7.0)
cT3-4N2-3	Appropriate (8.0)	Indeterminate (7.0)	Appropriate (8.0)	Indeterminate (7.0)

^a See Table 2 for details.

Table 4. Adjuvant Chemoradiotherapy^a

Stage	Proximal, No Major Symptoms	Proximal, Major Symptoms	Distal, No Major Symptoms	Distal, Major Symptoms
cT1N0	Inappropriate (1.5)	Inappropriate (1.5)	Inappropriate (2.0)	Inappropriate (2.0)
cT2N0	Indeterminate (3.5)	Indeterminate (3.5)	Disagreement (4.5)	Disagreement (4.5)
cT1-2N1	Appropriate (7.0)	Appropriate (7.0)	Indeterminate (7.0)	Indeterminate (7.5)
cT1-2N2-3	Appropriate (8.0)	Appropriate (8.0)	Necessary (7.0)	Necessary (7.0)
cT3-4N0	Appropriate (8.0)	Appropriate (8.0)	Necessary (7.0)	Necessary (7.0)
cT3-4N1	Appropriate (8.0)	Appropriate (8.0)	Necessary (7.0)	Necessary (7.0)
cT3-4N2-3	Appropriate (8.0)	Appropriate (8.0)	Necessary (7.0)	Necessary (7.0)

^a See Table 2 for details.

1 to 3, with agreement; and uncertain if the median rating was 4 to 6, with agreement. Agreement was met when 4 or fewer panelists rated outside the 3-point region containing the median (ie, 1-3, 4-6, or 7-9). Disagreement occurred when 4 or more panelists rated in each extreme 3-point region (ie, 1-3 or 7-9). Level of agreement was indeterminate when it failed to satisfy either criterion. The mean absolute deviation from the median, which reflects the degree of agreement, was also calculated for each score.⁹

Scenarios for which there was appropriate agreement were subsequently scored for necessity. Necessity was defined as “the expected health benefits exceeding the expected harms by such a margin that the service *must* be offered to the patient.”⁹ Necessity was scored in a similar manner as appropriateness and defined as necessary if the median rating was 7 to 9, with agreement; unnecessary if the median rating was 1 to 3, with agreement; and uncertain if the median rating was 4 to 6, with agreement. In the final classification, a scenario could be (1) necessary (appropriate and necessary), (2) appropriate (appropriate but unnecessary or uncertain necessity), (3) inappropriate (inappropriate on appropriateness score), (4) indeterminate (indeterminate on appropriateness score), (5) uncertain (uncertain agreement

on appropriateness score), or (6) disagreement (disagreement on appropriateness score). The final level of agreement reflects the median appropriateness and necessity scores, as well as the dispersion of the scoring (reflected by the mean absolute deviations from the median).

Results

Appropriateness and necessity scores are summarized in Tables 2 through 6 and eTables 1 through 6 in the Supplement.

Treatment of Curative GC

Initial Therapy

Surgical resection without preoperative therapy was considered appropriate for all Mo GC in proximal and distal tumors, with the exception of patients with T3-4N2-3 distal GC and minor symptoms. For these patients, the panel gave a mean appropriateness score of 7.5, with indeterminate agreement (Table 2). Necessity scores for these scenarios were high, especially for early-stage disease. The panelists believed surgical resection was necessary as initial therapy for most pa-

Table 5. Nonsurgical Management for Metastatic Gastric Carcinoma^a

Stage	Proximal, No Major Symptoms	Proximal, Major Symptoms	Distal, No Major Symptoms	Distal, Major Symptoms
M1—positive cytology	Disagreement (6.5)	Disagreement (5.0)	Disagreement (5.5)	Indeterminate (5.0)
M1—peritoneal carcinomatosis	Indeterminate (7.0)	Indeterminate (5.5)	Indeterminate (7.0)	Indeterminate (6.0)
M1—solitary liver metastasis	Indeterminate (7.0)	Indeterminate (5.5)	Disagreement (7.0)	Disagreement (5.0)
M1—more than 1 liver metastasis or more than 1 site of metastasis	Appropriate (8.0)	Indeterminate (5.5)	Appropriate (8.0)	Indeterminate (6.0)

^aSee Table 2 for details.Table 6. Gastrectomy for Metastatic Gastric Carcinoma^a

Stage	Proximal, No Major Symptoms	Proximal, Major Symptoms	Distal, No Major Symptoms	Distal, Major Symptoms
M1—positive cytology	Indeterminate (4.0)	Disagreement (5.0)	Disagreement (4.0)	Disagreement (6.0)
M1—peritoneal carcinomatosis	Inappropriate (2.0)	Indeterminate (3.0)	Inappropriate (3.5)	Indeterminate (5.0)
M1—solitary liver metastasis	Inappropriate (2.0)	Inappropriate (1.0)	Inappropriate (2.0)	Indeterminate (5.0)
M1—more than 1 liver metastasis or more than 1 site of metastasis	Inappropriate (1.0)	Indeterminate (2.0)	Inappropriate (1.0)	Indeterminate (2.0)

^aSee Table 2 for details.

tients with major symptoms. The panelists could not agree on the appropriateness of endoscopic mucosal resection for T1NO lesions, regardless of symptoms or location. They agreed it was inappropriate to perform endoscopic mucosal resection for all other scenarios (results not shown).

Perioperative chemotherapy was considered inappropriate for T1NO disease. For proximal and distal lesions and no major symptoms, perioperative chemotherapy was appropriate for T1-2N2-3 and T3-4N0-3 disease (Table 3). The appropriateness of perioperative chemotherapy for patients with major symptoms and advanced disease (>T2N0) was indeterminate.

Neoadjuvant chemoradiotherapy was inappropriate for all T1NO lesions and for asymptomatic distal T2NO lesions (eTable 1 in the Supplement). Panelists could not agree on the remaining scenarios (scores 2.0-7.0) (eTable 1 in the Supplement).

Postoperative Therapy

For T1NO disease, no adjuvant therapy was considered appropriate (eTable 2 in the Supplement). For T2NO disease, there was disagreement regarding no adjuvant therapy, while it was considered inappropriate for all other patients.

Adjuvant chemoradiotherapy was considered inappropriate following resection of T1NO disease (Table 4). For proximal lesions, adjuvant chemoradiotherapy was deemed appropriate for T1-2N1-3 or T3-4N0-3 disease. For distal cancers, adjuvant chemoradiation was classified as necessary for T1-2N2-3 and T3-4N0-3 disease.

The use of adjuvant chemotherapy following resection scored 7.0 to 7.5 for patients with distal GC and a more advanced stage, although agreement was not met (eTable 3 in the Supplement).

Surveillance

Appropriateness of surveillance imaging following gastrectomy was indeterminate (scores 4.0-5.0) (eTable 4 in the Supplement). There was disagreement over the appropriateness of imaging studies for only those patients who were symptomatic following gastrectomy. The panel believed it was appropriate to perform surveillance endoscopy following endoscopic resection; however, the appropriateness of surveillance endoscopy after gastrectomy was indeterminate.

Treatment of Metastatic GC

For the use of nonsurgical management, including stenting, in patients with metastatic GC without major symptoms, appropriateness scores were high but reached agreement only in patients with GC with more than 1 liver metastasis or more than 1 site of metastatic disease (Table 5). For patients with major symptoms, the appropriateness of nonsurgical management was indeterminate. Surgical resection was considered inappropriate for patients with no major symptoms unless the disease was limited to positive cytology alone, in which case there was disagreement regarding surgical management (Table 6).

Intraoperative Chemotherapy

The expert panel scored scenarios regarding the use of intra-peritoneal chemotherapy (IPC) for GC (eTables 5 and 6 in the Supplement). Appropriateness scores for the method of delivery of IPC, intraoperative and/or postoperative IPC, ranged from 5.0 to 5.5 (eTable 5 in the Supplement). Appropriateness scores for the indications for IPC ranged from 2.0 to 5.0, with most scoring inappropriate (eTable 6 in the Supplement). Agreement was reached that IPC was inappropriate for patients with GC and a peritoneal carcinomatosis index of more

than 20, those with peritoneal disease and either ovarian or solid organ metastasis, and patients who have undergone a multivisceral resection for T4 GC without peritoneal disease (eTable 6 in the Supplement).

Discussion

Differences in outcomes for patients with GC likely persist due to the complexity of decision making and lack of conclusive evidence regarding optimal care. In an attempt to address issues regarding the quality of care delivered to patients with GC, we assembled a multidisciplinary expert panel to define appropriate and necessary processes of care within a formal RAM process. The RAM process, a formal, validated method for developing measures of appropriate and necessary processes of care, has been used previously to study quality of care in oncology.²²⁻²⁴ There are several advantages of RAM over existing guidelines. The RAM process uses anonymous scoring, allows for differing levels of agreement between experts to be determined, and distinguishes between suggested and required care. The RAM process also allows delineation of treatment options that may be inappropriate, which is important given the potential harms to patients and the need for responsible resource allocation. The RAM process also gives a better understanding of areas of uncertainty, providing insight into the nuances in managing patients with GC and planning future trials.

The use of multimodality treatment to improve survival in patients with GC undergoing curative-intent resection is well established. In 2001, Macdonald et al³ reported a survival benefit with postoperative chemoradiation following surgery. In 2006, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial showed a survival benefit for patients receiving chemotherapy before and after surgery.² These 2 studies represent important therapeutic advances over surgery alone for GC. In addition, a meta-analysis using patient-level data has shown a survival advantage for adjuvant chemotherapy.⁴ However, since the comparator in all trials was surgery alone, and no direct comparison has been completed, the superior treatment regimen is unknown.²⁵ Given the complexities of these regimens and the potential for significant morbidity, it is important that treatment decisions be tailored to individual clinical scenarios. Case discussion at multidisciplinary cancer conferences is recommended and has been associated with improved treatment selection for patients with GC.²⁶ Overall, the expert panel supported perioperative chemotherapy and adjuvant chemoradiotherapy for patients with GC.

The use of perioperative chemotherapy is considered one standard of care for appropriately selected patients with GC.²⁵ Panelists agreed that perioperative chemotherapy was inappropriate for early-stage disease, consistent with criteria for the MAGIC trial.² In addition, perioperative chemotherapy may be appropriate for patients with bulky tumors or positive lymph nodes on perioperative staging investigations to assess response to therapy.²⁵ Patients with major symptoms—namely, bleeding requiring transfusion and/or obstruction—require im-

mediate surgical intervention and would not be candidates for perioperative chemotherapy. Interestingly, surgery without perioperative therapy was considered necessary for patients with distal GC with major symptoms and appropriate, but not necessary, for those with proximal GC with major symptoms. A recent US study showed that proximal GC was associated with higher use of perioperative therapy.⁷ It has been hypothesized that perioperative treatment is considered more strongly for proximal GC because of the increased complexity and morbidity of surgery.⁷

Adjuvant chemoradiation is also regarded as a standard of care in appropriately selected patients.²⁵ The use of adjuvant chemoradiotherapy was strongly supported by the expert panel and deemed necessary for patients with distal GC (>T1-2N1). Although there seems to be stronger support than that given to perioperative chemotherapy, the expert panel was asked to score adjuvant chemoradiation if no perioperative therapy was given, and therefore these patients were eligible only for adjuvant therapy. Regional differences are evident in existing guidelines, since adjuvant chemoradiotherapy is supported more widely in the United States than in the United Kingdom, Europe, or Asia.²⁷⁻²⁹ Ultimately, the decision to proceed with either perioperative chemotherapy or postoperative chemoradiation should be determined by discussion at multidisciplinary cancer conferences before resection.

Panelists agreed that postoperative chemoradiotherapy was not appropriate for patients with T1N0 disease and indeterminate for T2N0 when no preoperative therapy was given. Guidelines from the National Comprehensive Cancer Network suggest that perioperative therapy is not indicated in these patients, while adjuvant chemoradiotherapy may be considered for those with high-risk features, including poorly differentiated cancers, lymphovascular or neural invasion, high grade, or age younger than 50 years.²⁷ Japanese Gastric Cancer Association guidelines state that patients with T2N0 disease require no further therapy other than surgery.²⁹ Although the expert panel clearly identified no need for adjuvant therapy in T1N0 GC, the indeterminate finding for T2N0 GC emphasizes the need to consider more specific risk factors beyond stage to individualize care, ideally in the context of a multidisciplinary discussion.

There is no evidence that surveillance following curative therapy for GC affects survival.^{13,28} Proponents suggest surveillance may identify early recurrence, nutritional problems, and postgastrectomy symptoms, as well as provide psychosocial benefit.²⁸ The National Comprehensive Cancer Network guidelines recommend surveillance with history and physical examination with nutritional monitoring, while reserving imaging or endoscopy for symptomatic patients.²⁷ European Society for Medical Oncology guidelines suggest there are no indications for intensive follow-up, restricting visits to symptomatic patients alone.³⁰ Some authors suggest individual follow-up strategies may be carried out given that improved imaging technologies and development of improved systemic therapies were not accounted for in previous studies of surveillance.³¹ Panelists agreed surveillance endoscopy after endoscopic mucosal resection was appropriate but did not agree on surveillance recommendations otherwise.

The role of surgical management in patients with advanced, noncurative disease is debated.⁸ The National Comprehensive Cancer Network guidelines recommend palliative gastrectomy only for major symptoms.²⁷ The Japanese Gastric Cancer Association guidelines, however, advocate gastrectomy for patients with M1 disease without major symptoms, citing improvements in survival and the delay of symptoms as benefits.²⁹ To our knowledge, no randomized clinical trial exists to support or oppose the use of gastrectomy in patients with metastatic disease. The existing literature relies on retrospective data, with the potential for selection bias, and therefore comparisons of the effectiveness of noncurative surgery are difficult to interpret.⁸ Most important, significant risks exist with surgical intervention in patients with stage IV cancer.⁸ The expert panel deemed gastrectomy for patients with metastatic disease in the absence of symptoms as inappropriate.

Although surgery was not believed to be appropriate in patients with metastatic disease in the absence of major symptoms, agreement on the appropriateness of nonsurgical management was lacking (Table 5). A Cochrane review compared chemotherapy and best supportive care in a meta-analysis for patients with advanced GC and inoperable T4 cancers or M1 disease.³² This study concluded that chemotherapy provided a significantly increased survival benefit (hazard ratio, 0.37; 95% CI, 0.24-0.55).³² The role of surgery and chemotherapy in patients with metastatic GC warrants further study. The GYMSSA (Gastrectomy and Metastectomy plus Systemic therapy vs Systemic therapy Alone) and REGATTA (REductive Gastrectomy for Advanced Tumor in Two Asian countries) trials are currently under way, with the aim to identify patient selection factors for gastrectomy in the presence of limited metastatic disease.^{33,34} In the interim, chemotherapy and surgery for metastatic GC should be considered individually and in the setting of a multidisciplinary discussion.

The expert panel was asked to score appropriateness and necessity scores regarding IPC for GC, including the type of therapy and indications for use. No scenarios on the type of IPC were considered appropriate, and these scores reflect the uncertainty regarding this treatment. A systematic review and meta-analysis on IPC for patients with GC found an association with improved survival for heated IPC alone (hazard ratio, 0.60; 95% CI, 0.43-0.83; $P = .002$) or with early postoperative normothermic IPC (hazard ratio, 0.45; 95% CI, 0.29-0.68; $P < .001$).³⁵ These trials, designed to prevent peritoneal dissemination, were not advocated as a treatment of metastatic disease. Most important, IPC is associated with significant mor-

idity. Yang and colleagues³⁶ have published the results of a small randomized clinical trial that shows improved median survival for patients with GC and synchronous peritoneal carcinomatosis treated with IPC. Further research is required to support the findings of a single, small study. While no agreement was met on appropriate indications for IPC, lower appropriateness scores were observed in patients with increasing burden of peritoneal disease. The expert panel scores recognize the lack of a definitive evidence of benefit, which would require a properly designed multicenter randomized clinical trial.³⁵

There are several limitations to this study. Although an extensive and rigorous review of the literature was provided to the panel, most data were gathered from retrospective studies. In addition, during the RAM process, the opinion of the experts becomes more influential in scenarios where there is a paucity of evidence from high-quality studies. The preponderance of surgical experts, especially surgical oncologists, among the membership of the panel may have biased the outcome of the RAM process. However, since our focus was on surgical aspects of GC management, the panel was purposefully weighted toward more surgeons. In addition, although previous studies have shown the importance of multidisciplinary representation, similar results tend to occur regardless of exact panel composition.⁹ Finally, many members of the expert panel were constituted from tertiary, academic centers, which may limit the understanding of the challenges facing physicians in hospitals with fewer resources and lower case volumes. In North America, most cancer care occurs in community hospitals, and attempts were made to introduce this perspective during the discussions.

In conclusion, an international, multidisciplinary expert panel has identified the processes of care that are appropriate and necessary for treating patients with GC. The use of chemotherapy and chemoradiation is recommended for patients with curative-intent GC and tumors with a stage of T2NO or higher. Surgery for metastatic disease should be considered only for major symptoms. Surveillance following curative therapy for GC is appropriate for patients who have undergone endoscopic resection; otherwise, there was no agreement on the use of regular surveillance in these patients. To our knowledge, these guidelines are the first to be developed for patients with GC using the RAM process and will aid in multidisciplinary treatment decisions, including patients with metastatic disease. Furthermore, these processes of care may also be used to identify areas for quality improvement in patients with GC.

ARTICLE INFORMATION

Accepted for Publication: July 22, 2013.

Published Online: November 13, 2013.
doi:10.1001/jamasurg.2013.3959.

Author Affiliations: Department of Surgery, University of Toronto, Toronto, Ontario, Canada (Brar, Swallow, Law, McLeod, Coburn); Department of Community Health and Epidemiology, Queen's University, Kingston, Ontario, Canada (Mahar); Sunnybrook Research Institute, Toronto, Ontario, Canada (Mahar, Seevaratnam, Cardoso, Bociariu,

Coburn); Department of Surgery, Dalhousie University, Halifax, Canada (Helyer, Porter); Institute for Clinical Effectiveness Studies, Toronto, Ontario, Canada (Paszat, Earle, Coburn); Department of Surgery, Maimonides Medical Center, Brooklyn, New York (Dixon); Department of Surgery, Brown University, Providence, Rhode Island (Yohanathan, Miner); Department of Gastroenterology Surgery, São Paulo Federal University, São Paulo, Brazil (Lourenco); Departments of Medicine and Pharmacology, Ohio State University, Columbus (Bekaii-Saab);

Department of Medicine, Royal Marsden Hospital, Sutton, Surrey, United Kingdom (Chau); Department of Surgery, University of Calgary, Calgary, Alberta, Canada (Church); Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York (Coit); Department of Radiation Oncology, MD Anderson Cancer Center, Houston, Texas (Crane); Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Earle, Marcon); Department of Surgical Oncology, MD Anderson Cancer Center, Houston, Texas (Mansfield); Department of Surgery, Yonsei

University College of Medicine, Seoul, South Korea (Noh); Department of Surgery, University of Chicago, Chicago, Illinois (Posner, Prachand); Department of Surgery, Cancer Institute Hospital, Tokyo, Japan (Sano); Department of Surgery, Leiden University Medical Centre, Leiden, the Netherlands (van de Velde); Department of Surgery, University of Michigan Health System, Ann Arbor (Wong).

Author Contributions: Drs Brar and Coburn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Helyer, Swallow, Law, Paszat, Chau, Crane, Sano, Coburn.

Acquisition of data: Brar, Mahar, Helyer, Paszat, Seevaratnam, Cardoso, Dixon, Yohanathan, Lourenco, Bekaili-Saab, Chau, Church, Coit, Crane, Earle, Mansfield, Miner, Porter, Posner, Prachand, Wong, Coburn.

Analysis and interpretation of data: Brar, Mahar, Paszat, Cardoso, McLeod, Dixon, Bocicariu, Bekaili-Saab, Chau, Coit, Earle, Mansfield, Marcon, Noh, Porter, Posner, Van de Velde, Wong, Coburn.

Drafting of the manuscript: Brar, Helyer, Law, Cardoso, Dixon, Yohanathan, Bocicariu, Bekaili-Saab, Posner, Van de Velde, Coburn.

Critical revision of the manuscript for important intellectual content: Brar, Mahar, Swallow, Paszat, Seevaratnam, Cardoso, McLeod, Dixon, Lourenco, Bocicariu, Bekaili-Saab, Chau, Church, Coit, Crane, Earle, Mansfield, Marcon, Miner, Noh, Porter, Prachand, Sano, Wong, Coburn.

Statistical analysis: Brar, Law, Seevaratnam, Cardoso, Dixon, Bocicariu, Coburn.

Obtained funding: Paszat, Coburn.

Administrative, technical, and material support: Brar, Mahar, Law, Cardoso, Dixon, Yohanathan, Marcon, Miner, Porter, Prachand, Coburn.

Study supervision: Paszat, McLeod, Lourenco, Coit, Noh, Sano, Van de Velde, Coburn.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by grant O19325 from the Canadian Cancer Society, the Ontario Ministry of Health and Long-Term Care (Drs Coburn and Paszat), and the Hanna Family Research Chair in Surgical Oncology (Dr Law).

Role of the Sponsor: The fundings sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentations: This paper was presented at the Gastrointestinal Cancers Symposium 2012; January 19, 2012; San Francisco, California, and the Society of Surgical Oncology Annual Cancer Assembly; March 21, 2012; Orlando, Florida.

Additional Contributions: The National Health Service provided funding to the National Institute for Health Research's Biomedical Research Centre (Dr Chau).

REFERENCES

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.
- Cunningham D, Allum WH, Stenning SP, et al; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.
- Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345(10):725-730.
- Paoletti X, Oba K, Burzykowski T, et al; GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA*. 2010;303(17):1729-1737.
- Sakuramoto S, Sasako M, Yamaguchi T, et al; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357(18):1810-1820.
- Coburn NG, Lourenco LG, Rossi SE, et al. Management of gastric cancer in Ontario. *J Surg Oncol*. 2010;102(1):54-63.
- Sherman KL, Merkow RP, Bilimoria KY, et al. Treatment trends and predictors of adjuvant and neoadjuvant therapy for gastric adenocarcinoma in the United States. *Ann Surg Oncol*. 2013;20(2):362-370.
- Mahar AL, Coburn NG, Singh S, Law C, Helyer LK. A systematic review of surgery for non-curative gastric cancer. *Gastric Cancer*. 2012;15(suppl 1):S125-S137.
- Fitch K. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND Corp; 2001.
- Brar SS, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. A systematic review of spleen and pancreas preservation in extended lymphadenectomy for gastric cancer. *Gastric Cancer*. 2012;15(suppl 1):S89-S99.
- Cardoso R, Bocicariu A, Dixon M, et al. What is the accuracy of sentinel lymph node biopsy for gastric cancer? a systematic review. *Gastric Cancer*. 2012;15(suppl 1):S48-S59.
- Cardoso R, Coburn N, Seevaratnam R, et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. *Gastric Cancer*. 2012;15(suppl 1):S19-S26.
- Cardoso R, Coburn NG, Seevaratnam R, et al. A systematic review of patient surveillance after curative gastrectomy for gastric cancer: a brief review. *Gastric Cancer*. 2012;15(suppl 1):S164-S167.
- Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer*. 2012;15(suppl 1):S38-S47.
- Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. *Gastric Cancer*. 2012;15(suppl 1):S27-S37.
- Mahar AL, Coburn NG, Karanickolas PJ, Viola R, Helyer LK. Effective palliation and quality of life outcomes in studies of surgery for advanced, non-curative gastric cancer: a systematic review. *Gastric Cancer*. 2012;15(suppl 1):S138-S145.
- Mahar AL, McLeod RS, Kiss A, et al. A systematic review of the effect of institution and surgeon factors on surgical outcomes for gastric cancer. *J Am Coll Surg*. 2012;214(5):860-868.
- Raziee HR, Cardoso R, Seevaratnam R, et al. Systematic review of the predictors of positive margins in gastric cancer surgery and the effect on survival. *Gastric Cancer*. 2012;15(suppl 1):S116-S124.
- Roberts P, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. Systematic review of pancreaticoduodenectomy for locally advanced gastric cancer. *Gastric Cancer*. 2012;15(suppl 1):S108-S115.
- Seevaratnam R, Bocicariu A, Cardoso R, et al. How many lymph nodes should be assessed in patients with gastric cancer? a systematic review. *Gastric Cancer*. 2012;15(suppl 1):S70-S88.
- Brook RH, Chassin MR, Fink A, Solomon DH, Koseoff J, Park RE. A method for the detailed assessment of the appropriateness of medical technologies. *Int J Technol Assess Health Care*. 1986;2(1):53-63.
- Bilimoria KY, Bentrem DJ, Lillemoe KD, Talamonti MS, Ko CY; Pancreatic Cancer Quality Indicator Development Expert Panel, American College of Surgeons. Assessment of pancreatic cancer care in the United States based on formally developed quality indicators. *J Natl Cancer Inst*. 2009;101(12):848-859.
- Bilimoria KY, Raval MV, Bentrem DJ, Wayne JD, Balch CM, Ko CY. National assessment of melanoma care using formally developed quality indicators. *J Clin Oncol*. 2009;27(32):5445-5451.
- McGory ML, Shekelle PG, Ko CY. Development of quality indicators for patients undergoing colorectal cancer surgery. *J Natl Cancer Inst*. 2006;98(22):1623-1633.
- Knight G, Earle CC, Cosby R, et al; Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable gastric cancer: a systematic review and practice guideline for North America. *Gastric Cancer*. 2013;16(1):28-40.
- Davies AR, Deans DA, Penman I, et al. The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer. *Dis Esophagus*. 2006;19(6):496-503.
- Ajani JA, Barthel JS, Bekaili-Saab T, et al; NCCN Gastric Cancer Panel. Gastric cancer. *J Natl Compr Canc Netw*. 2010;8(4):378-409.
- Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2011;60(11):1449-1472.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer*. 2011;14(2):113-123.
- Okines A, Verheij M, Allum W, Cunningham D, Cervantes A; ESMO Guidelines Working Group. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v50-v54.
- Van Cutsem E, Dicato M, Geva R, et al. The diagnosis and management of gastric cancer: expert discussion and recommendations from the 12th ESMO/World Congress on Gastrointestinal Cancer, Barcelona, 2010. *Ann Oncol*. 2011;22(suppl 5):v1-v9.

32. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. *Cochrane Database Syst Rev*. 2010;(3):CD004064. doi:10.1002/14651858.CD004064.pub3.

33. Fujitani K, Yang HK, Kurokawa Y, et al; Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group; Korea Gastric Cancer Association. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical

Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. *Jpn J Clin Oncol*. 2008;38(7):504-506.

34. Kerkar SP, Kemp CD, Duffy A, et al. The GYMSSA trial: a prospective randomized trial comparing gastrectomy, metastasectomy plus systemic therapy versus systemic therapy alone. *Trials*. 2009;10:121. doi:10.1186/1745-6215-10-121.

35. Yan TD, Black D, Sugarbaker PH, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant

intraperitoneal chemotherapy for resectable gastric cancer. *Ann Surg Oncol*. 2007;14(10):2702-2713.

36. Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol*. 2011;18(6):1575-1581.

Invited Commentary

Sometimes Consensus and Expert Opinion Is the Best We Can Do

Richard D. Schulick, MD, MBA

Brar et al,¹ assembling a multidisciplinary expert panel of 16 physicians from 6 countries, follow the RAND/UCLA Appropriateness Method to try to define optimal treatment strategies for gastric adenocarcinoma. The strengths of this process are that it distinguishes between suggested



Related article page 18

and required care and defines which treatment options may be inappropriate. This study is helpful because it provides a summary of the agreement and disagreement of certain therapeutic options. We must remember that these guidelines are built by current thoughts and procedures and thus are heavily biased. To illustrate this point, had we assembled an expert panel on the use of lumpectomy for breast cancer several decades ago, the results would probably not reflect our

current approach, which has been established by multiple high-level randomized clinical trials, some with counterintuitive results.² Nonetheless, the group does represent a strong body of knowledge and expertise on the subject of gastric cancer and provides a nice summary of the current body of knowledge.

Brar et al¹ state that gastric cancer is responsible for 10% of all cancer deaths worldwide—making it a significant killer. It is interesting that we have seen the completion of many randomized clinical trials for breast cancer that have affected the treatment of this disease but only a few for gastric cancer.² Perhaps it is because the disease is less common in developed and Western countries. I hope the expert panelists take this opportunity to try to scientifically study some of their areas of disagreement with appropriate clinical trials so that we can advance the field and discover what is best for our patients.

ARTICLE INFORMATION

Author Affiliation: Department of Surgery, University of Colorado, Aurora.

Corresponding Author: Richard D. Schulick, MD, MBA, Department of Surgery, University of Colorado, 12631 E 17th Ave, Mail Stop C-305, Academic Office One Building, Room 6117, Aurora, CO 80045 (richard.schulick@ucdenver.edu).

Published Online: November 13, 2013. doi:10.1001/jamasurg.2013.3987.

Conflict of Interest Disclosures: None reported.

REFERENCE

1. Brar SS, Mahar AL, Helyer LK, et al. Processes of care in the multidisciplinary treatment of gastric

cancer: results of a RAND/UCLA expert panel [published online November 13, 2013]. *JAMA Surg*. doi:10.1001/jamasurg.2013.3959.

2. Mamounas EP. NSABP breast cancer clinical trials: recent results and future directions. *Clin Med Res*. 2003;1(4):309-326.