Research article

**Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a clinical practice guideline**

Richard A Malthaner¹, Rebecca KS Wong², R Bryan Rumble*³, Lisa Zuraw³ and members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care

Address: ¹University of Western Ontario, London Health Sciences Centre Division of Thoracic Surgery and Surgical Oncology, London, Ontario, Canada, ²Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada and ³Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada

Email: Richard A Malthaner - richard.malthaner@lhsc.on.ca; Rebecca KS Wong - rebecca.wong@rmp.uhn.on.ca; R Bryan Rumble* - rumbleb@mcmaster.ca; Lisa Zuraw - rumble@mcmaster.ca; members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario’s Program in Evidence-based Care - rumbleb@mcmaster.ca

* Corresponding author

**Abstract**

**Background:** Carcinoma of the esophagus is an aggressive malignancy with an increasing incidence. Its virulence, in terms of symptoms and mortality, justifies a continued search for optimal therapy. A clinical practice guideline was developed based on a systematic review investigating neoadjuvant or adjuvant therapy on resectable thoracic esophageal cancer.

**Methods:** A systematic review with meta-analysis was developed and clinical recommendations were drafted. External review of the practice guideline report by practitioners in Ontario, Canada was obtained through a mailed survey, and incorporated. Final approval of the practice guideline was obtained from the Practice Guidelines Coordinating Committee.

**Results:** The systematic review was developed and recommendations were drafted, and the report was mailed to Ontario practitioners for external review. Ninety percent of respondents agreed with both the evidence summary and the draft recommendations, while only 69% approved of the draft recommendations as a practice guideline. Based on the external review, a revised document was created. The revised practice guideline was submitted to the Practice Guidelines Coordinating Committee for review. All 11 members of the PGCC returned ballots. Eight PGCC members approved the practice guideline report as written and three members approved the guideline conditional on specific concerns being addressed. After these recommended changes were made, the final practice guideline report was approved.

**Conclusion:** In consideration of the systematic review, external review, and subsequent Practice Guidelines Coordinating Committee revision suggestions, and final approval, the Gastrointestinal Cancer Disease Site Group recommends the following:

For adult patients with resectable thoracic esophageal cancer for whom surgery is considered appropriate, surgery alone (i.e., without neoadjuvant or adjuvant therapy) is recommended as the standard practice.
Background
Carcinoma of the esophagus is an aggressive malignancy with an increasing incidence. Its virulence, in terms of symptoms and mortality, justifies a continued search for optimal therapy. The large and growing number of patients affected, the high mortality rates, the worldwide geographic variation in practice, and the large body of good quality research warrants a clinical practice guideline.

This clinical practice guideline was developed by the Gastrointestinal Cancer Disease Site Group (DSG) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle [1]. This practice guideline report is a convenient and up-to-date source of the best available evidence on neoadjuvant or adjuvant therapy for resectable esophageal cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical practice guideline information.

The systematic review on neoadjuvant or adjuvant therapy for resectable esophageal cancer, which forms the basis for this clinical practice guideline, is available in a companion document [2]. Based on the systematic review, draft recommendations were developed by consensus of the Gastrointestinal Cancer DSG to create the clinical practice guideline report. The clinical practice guideline is intended to promote evidence-based practice in Ontario, Canada. As part of the PEBC’s clinical Practice Guideline Development Cycle, all draft recommendations are sent to Ontario practitioners for external review. The efficacy of this external review process has been previously described [3]. The external review is a mailed survey consisting of items that address the quality of the draft practice guideline report and draft recommendations and whether the draft recommendations should serve as a practice guideline. Final approval of this practice guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

Methods
Clinical practice guideline development

Systematic review
A systematic review with meta-analysis on neoadjuvant or adjuvant therapy for resectable esophageal cancer was developed by the Gastrointestinal Cancer DSG of Cancer Care Ontario’s Program in Evidence-based Care [2]. The evidence examined did not support the use of neoadjuvant or adjuvant chemotherapy or radiotherapy for resectable thoracic esophageal cancer.

Gastrointestinal cancer disease site group consensus
In discussions regarding the completed systematic review, the Gastrointestinal Cancer DSG agreed that the evidence did not support a recommendation for neoadjuvant or adjuvant chemotherapy or radiotherapy for resectable thoracic esophageal cancer. A recommendation that surgery alone should be the standard of care for this patient population was drafted, and it was recommended that the draft practice guideline be sent out to Ontario practitioners for external review.

The role of radiotherapy alone and chemoradiation alone without surgery is addressed in a separate Gastrointestinal Cancer DSG Clinical Practice Guideline: Combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus [4].

Results
External review
Practitioner feedback was obtained through a mailed survey of 163 practitioners in Ontario (27 medical oncologists, 21 radiation oncologists, 112 surgeons, and three gastroenterologists). The survey consisted of items evaluating the methods, results, and interpretative summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

Eighty-six surveys (58%) were returned. Twenty-nine respondents (34%) (nine medical oncologists, seven radiation oncologists, and 13 surgeons) indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized below.

1. Number surveyed: 163 practitioners in Ontario, Canada involved in the care of cancer patients
2. Return rate: 58% (mean Gastrointestinal Cancer DSG return rate: 60.2%; range: 51% – 84%)
3. Written comments attached: 10%
4. Agreement with the summary of evidence: 90%
5. Agreement with the recommendation: 90%
6. Approval of the recommendation as a practice guideline: 69%
Summary of main findings

Three (10%) respondents provided written comments. One practitioner hypothesized that preoperative chemoradiation might have a role in adenocarcinoma of the lower third of the esophagus (as suggested by Walsh et al [5] with 100% adenocarcinoma and by Urba et al [6] with 75% adenocarcinoma), but not in squamous cell carcinoma (as suggested by Bosset et al [7] and by Le Prise et al [8]). Another respondent noted that the survival advantage at three years for combined treatment for preoperative chemoradiotherapy is discounted in the guideline report, and suggested that the guideline recommend the selection of the option preferred by informed patients. There was a request for an algorithm to help in deciding between surgical and non-surgical treatment. The same respondent commented on the limited discussion on quality of life. Two radiation oncologists disagreed with the recommendations and thought that the draft practice guideline report should not be approved as a practice guideline, but neither provided written comments.

Discussion

Gastrointestinal cancer disease site group modifications and actions

After completion of the practitioner feedback survey, additional trials were found. The results of two randomized trials both found surgery alone to be significantly superior to radiation alone [9,10], which resulted in an original draft recommendation regarding radiation alone as a primary modality for localized esophageal cancer being removed from the final practice guideline.

In response to this feedback, the Gastrointestinal Cancer DSG acknowledged that the majority of studies have been performed in squamous cell carcinomas. While adenocarcinomas were included in some studies, a distinction between the two histological subtypes was not made because previous studies have not consistently found that they respond differently to chemotherapy or radiation, and nine references [11-19] were added to support this. The Gastrointestinal Cancer DSG did not feel the evidence was compelling enough to recommend preoperative chemoradiotherapy over surgery alone based on the three-year data. After consideration, the Gastrointestinal Cancer DSG decided not to create an algorithm as suggested as a similar project is currently under development.

After addressing the comments obtained from practitioners during the external review, the Gastrointestinal Cancer DSG voted that the overall guideline recommendations should be approved, and submitted the practice guideline to the Practice Guidelines Coordinating Committee for review.

Practice guidelines coordinating committee approval process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee for review and approval. All 11 members of the PGCC returned ballots. Eight PGCC members approved the practice guideline report as written and three members approved the guideline conditional on the Gastrointestinal Cancer DSG addressing specific concerns. PGCC members requested that the following issues be addressed prior to the approval of the guideline report:

One member noted that although the majority of studies had been performed in squamous cell carcinomas, some studies included adenocarcinomas, and it would be helpful if the pathological subtypes were discussed. In particular, this member wanted to know if there was any difference in response or outcome for the two histological subtypes. Another member noted that although the pooled analysis for preoperative chemoradiation versus surgery alone detected no difference at one year, the pooled estimate almost reached significance. This member was concerned that the discussion may be too dismissive of the data, and suggested there be some acknowledgment that further follow-up and additional studies are needed.

In response to this feedback, the Gastrointestinal Cancer DSG expanded on the earlier revisions concerning the similarities in response to treatment between squamous cell carcinomas and adenocarcinomas.

Also, after the original practice guideline was submitted to the PGCC, two meta-analyses [20,21] both detecting a statistically significant difference in survival at three years favouring preoperative chemoradiation versus surgery alone were obtained. The Gastrointestinal Cancer DSG re-pooled the mortality data from the six trials [3-8,22,23] at three years and obtained similar results.

Conclusions

In consideration of the systematic review, external review, and subsequent Practice Guidelines Coordinating Committee revision suggestions, and final approval, the Gastrointestinal Cancer Disease Site Group developed the following Clinical Practice Guideline:

Practice guideline

This practice guideline reflects the most current information reviewed by the Gastrointestinal Cancer DSG.

Target population

These recommendations apply to adult patients with resectable and potentially curable thoracic (lower two-
thirds of esophageal cancer for whom surgery is considered appropriate.

**Recommendation**

- If surgery is considered appropriate, then surgery alone (i.e., without neoadjuvant or adjuvant therapy) is recommended as the standard practice for resectable thoracic esophageal cancer.

This Clinical Practice Guideline report is based on work completed in October, 2003. All approved PEBC Clinical Practice Guideline reports are updated regularly. Please see the PEBC’s web site [http://www.cancercare.on.ca/access_PEBC.htm](http://www.cancercare.on.ca/access_PEBC.htm) for a complete list of current and ongoing projects.

**Competing interests**

The author(s) declare that they have no competing interests.

**List of abbreviations used**

In order of appearance:

DSG, Disease Site Group; PEBC, Program in Evidence-based Care; PGCC, Practice Guidelines Coordinating Committee.

**Authors’ contributions**

RM, RW, and LZ created the initial drafts of this clinical practice guideline with input from other members of the Gastrointestinal Cancer DSG. RM, RW, and BR created the final draft of this clinical practice guideline. Creation of the submitted manuscript was performed by BR and RM.

**Acknowledgements**

Additional members of Cancer Care Ontario’s Program in Evidence-based Care Practice Guidelines Initiative’s Gastrointestinal Cancer Disease Site Group include: O. Agboola MD, M. Citron, F.G. DeNardi MD, S. Fine MD, B. Fisher MD, C. Germond MD, D. Jonker MD, K. Khoo MD, W. Kocha MD, M. Lethbridge, W. Lofers MD, and V. Tandan MD. Please see the Practice Guidelines Initiative (PGI) web site [http://www.cancercare.on.ca/access_PEBC.htm](http://www.cancercare.on.ca/access_PEBC.htm) for a complete list of current and past Disease Site Group members.

**References**

1. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KLJ, Gafni A, Laupacis A: The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995, 13:502-512.
2. Malthaner RA, Wong RKS, Rumble RB, Zuraw L, members of the Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario’s Program in Evidence-based Care: Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. BMC Medicine 2004, 2:35.
3. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KLJ, Evans WK, Maroun JA, Hodgson DI, Carey MS, Cowan DH: Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol 1998, 16:1226-1231.
4. Wong RK, Malthaner RA, Zuraw L, Rumble RB, the Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group: Combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus: a practice guideline. Int J Radiat Oncol Biol Phys 2003, 55(4):930-942.
5. Walsh TN, Noonan N, Hollywood D, Kelly A, Keelings N, Hennessy TP: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996, 335:462-467.
6. Urbas SG, Orringer MB, Turcios A, Iannettoni MD, Paul AR, Lash TL, Stewart F: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001, 19:305-313.
7. Bosset JF, Gignoux M, Triboulet JP, Tirtet E, Mantion G, Elias D, Lozach P, Ollier JC, Pay C, Mercier M, Sahmoud T: Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997, 337:161-167.
8. Le Piére E, Etienne PL, Meunier B, Madao G, Ben Hassel M, Gedouin F, Mornex F: The quality of swallowing for patients with operable esophageal carcinoma. Cancer 1999, 85:763-768.
9. Forastiere AA, Orringer MB, Perez-Tamayo C, Urbas SG, Husted S, Takusagi BJ, Zahurak M: Concurrent chemotherapy and radiation therapy followed by transhiatal esophagectomy for local-regional cancer of the esophagus. J Clin Oncol 1990, 8:119-127.
10. Coia LR, Engstrom PF, Paul AR, Staffard PM, Hanks GE: Long-term results of infusional 5-FU, mitomycin-C and radiation as primary management of esophageal carcinoma. Int J Radiat Oncol Biol Phys 1991, 30:29-36.
11. Forastiere AA: Treatment of locoregional esophageal cancer. Semin Oncol 1992, 19:57-63.
12. Gill PG, Denham JW, Jameson GG, Dewitt PG, Yeo E, Olweny C: Patterns of treatment failure and prognostic factors associated with the treatment of esophageal carcinoma with chemotherapy and radiotherapy either as sole treatment or followed by surgery. J Clin Oncol 1992, 10:1037-1043.
13. Naunheim KS, Petruska P, Roy TS, Andrus CH, Johnson FE, Schlueter JM, Baue AE: Preoperative chemotherapy and radiotherapy for esophageal carcinoma. J Thorac Cardiovasc Surg 1992, 103:887-893.
14. Jones DR, Dettberbeck FC, Egan TM, Parker LA Jr, Bernard SA, Tepper JE: Induction chemoradiotherapy followed by esophagectomy in patients with carcinoma of the esophagus. Ann Thorac Surg 1997, 64:185-191.
15. Ilson DH, Ajani J, Bhatla K, Forastiere A, Huang Y, Patel P, Martin L, Donegan J, Pazdur R, Reed C, Kelsen DP: Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998, 16:1826-1834.
16. Orringer MB, Marshall B, Langanos MD: Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999, 230:392-400.
17. Altorki NK: Three-field lymphadenectomy for esophageal cancer. Chest Surg Clin N Am 2000, 10:553-560.
18. Ceccherini JD, Vasan H: A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery for esophageal cancer alone for resectable esophageal cancer. Am J Surg 2003, 185:538-543.
19. Ngaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, Mantyla M, Modig H, Munk-Wijkstra E, Rosengren B, Tausje J, Elek K: Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 1992, 16:1104-1109.
Pre-publication history
The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2407/4/67/prepub