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Evidence-based Series 2-12 Version 2- EDUCATION AND INFORMATION 2015

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus

Members of the Gastrointestinal Cancer Disease Site Group.

An assessment conducted in October 2015 placed Evidence-based Series (EBS) 2-12 Version 2 in the EDUCATION AND INFORMATION section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Evidence-based Series (EBS) 2-12 Version 2, the full review report, consists of the following 4 parts:

1. **Guideline Overview**
2. **Summary**
3. **Full Report**
4. **Document Assessment and Review Tool**

and is available on the CCO website on the PEBC Gastrointestinal Cancer DSG page

Report Date: October 17, 2013

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Evidence-based Series 2-12 Version 2

Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Apr 2002	1966 to 2001	Full Report	Peer review publication[1] Web publication	Not Applicable
Update Jun 2003	2001 to 2003	New data added to original Full Report	Updated Web publication	Literature search updated in February 2005
Version 2 Sep 2011	2005 to 2010	New data found in Document Assessment and Review Tool	Updated Web publication	2003 Guideline Recommendations ENDORSED

1 Wong RKS, Malthaner RA, Zuraw L, Rumble RB, and 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. Int J Radiat Oncol Biol Phys. 2003; 55(4): 930-42.

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Evidence-based Series 2-12 Version 2

Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus

Guideline Review Summary

Review Date: September 29, 2010

The 2003 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2002 and its first update released in June 2003. In September 2010, the PEBC guideline update strategy was applied, and the new updated document released in September 2011. The Summary and the Full Report in this version are the same as in the June 2003 version.

Update Strategy

Using the Document Assessment and Review Tool at the end of this report, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

Does combined modality radiotherapy and chemotherapy improve survival compared with radiotherapy alone in patients with localized carcinoma of the esophagus for whom a non-surgical approach is used?

Literature Search and New Evidence

The new search (February 2005 to July 2010) yielded one relevant new publications (a conference abstract). Brief results of this publication are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations for combined modality radiotherapy and chemotherapy in the non-surgical management of localized carcinoma of the esophagus. Hence, the Gastrointestinal Cancer DSG **ENDORSED** the 2003 recommendations.

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Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus

Practice Guideline Report #2-12

Wong RKS, Malthaner RA, Zuraw L, Rumble RB, and members of Cancer Care Ontario's Program in Evidence-based Care's Gastrointestinal Cancer Disease Site Group

Please see the EBS 2-12 Version 2 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2010.

Report Date: February 10, 2005

SUMMARY

Guideline Question

Does combined modality radiotherapy and chemotherapy improve survival compared with radiotherapy alone in patients with localized carcinoma of the esophagus for whom a non-surgical approach is used?

Target Population

These recommendations apply to adult patients with localized (T1-3, small volume N1, M0) carcinoma of the esophagus and good performance status who are considering a non-surgical approach and for whom combined radiotherapy and chemotherapy can be tolerated in the judgment of the treating oncologist.

Recommendations

- Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice pattern and the currently available research evidence, a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used.
- Patients should be made aware of the increased acute toxicity associated with this approach. The decision to use concomitant radiotherapy and chemotherapy should only be made after careful consideration of the potential risks, benefits, and the patient's general condition.

- Sequential radiotherapy and chemotherapy is not recommended as standard practice.
- Future clinical trials to better define the optimal chemoradiotherapy combination that would improve outcomes while limiting toxicities are strongly encouraged.

Methods

Entries to MEDLINE (1966 through February week 1, 2005), EMBASE (1996 through week 6, 2005), CANCERLIT (1983 through October 2001), and Cochrane Library (2004, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology through 2004 were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which comprises medical and radiation oncologists, surgeons, a pathologist, and patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- A pooled analysis of seven randomized trials involving a total of 687 patients detected a statistically significant survival benefit at one year for concomitant radiotherapy and chemotherapy compared with radiotherapy alone (one-year mortality odds ratio, 0.61; 95% confidence interval, 0.44 to 0.84; $p<0.00001$). Local control is also significantly improved with concomitant radiotherapy and chemotherapy compared with radiotherapy alone where data are available (odds ratio, 0.52; 95% confidence interval, 0.31 to 0.89; $p=0.004$). Concomitant radiotherapy and chemotherapy is associated with a significant increase in adverse effects, including life-threatening toxicities, compared with radiotherapy alone.

Related Guidelines

Practice Guideline Initiative's Practice Guideline #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.

For further information about this practice guideline report, please contact Dr. Jean Maroun, Chair, Gastrointestinal Cancer Disease Site Group, Ottawa Regional Cancer Centre, General Division, 503 Smyth Road, Ottawa, Ontario, K1H 1C4, (613) 737-7700, ext. 6708, FAX (613) 247-3511.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit www.cancercare.on.ca for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:
[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO Web site at:
http://www.cancercare.on.ca
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Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

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Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus

Practice Guideline Report #2-12

Wong RKS, Malthaner RA, Zuraw L, Rumble RB, and members of Cancer Care Ontario's Program in Evidence-based Care's Gastrointestinal Cancer Disease Site Group

Please see the EBS 2-12 Version 2 Guideline Review Summary and the Document Assessment and Review Tool for the summary of updated evidence published between 2005 and 2010.

Report Date: February 10, 2005

FULL REPORT

I. QUESTION

Does combined modality radiotherapy and chemotherapy improve survival compared with radiotherapy alone in patients with localized carcinoma of the esophagus for whom a non-surgical approach is used?

II. CHOICE OF TOPIC AND RATIONALE

Carcinoma of the esophagus has a poor overall prognosis. The extent of disease at the time of presentation and a patient's performance status are the most powerful predictors of the potential for cure (1,2). The opportunity exists to eradicate the disease that is localized at presentation through therapy given with curative intent. The current TNM (Tumour Node Metastases) staging system (6th edition 2002) (3) incorporated major prognostic factors, including the extent of esophageal wall involvement (T1-4) and whether local regional nodes are involved (N1). The extent of disease that oncologists consider amenable to curative intent is evolving. The changes in the precision and accuracy of diagnostic modalities, including the use of tools such as minimally invasive staging techniques, are improving the accuracy of clinical staging. Within this context, most would consider patients with T4 disease and extensive nodal involvement incurable. There is increasing evidence that patients with less than five nodes involved may have a better outcome than those with more extensive disease (4). Furthermore, the definition of nodal stations that are considered regional and still amenable to potentially curative therapies is also evolving. For the purpose of this guideline, patients with T1-3, small volume N1, M0 are considered potential candidates for curative therapy.

Both primary surgery and radiotherapy (RT) are offered as treatment options to suitable candidates. In cervical tumours, the desire to avoid a laryngoesophagectomy, together with the

retrospective data supporting a better prognosis with cervical esophageal tumours, has resulted in the general acceptance of an organ-preserving approach for these patients. For patients with thoracic esophageal tumours, the recommendation for a primary surgical approach versus a primary radiotherapy approach had predominantly been based on the patient's medical operability, the patient's preference, and the treating physician's estimation of the relative morbidity of the outcomes. A well-known attempt in the United Kingdom to compare surgery and radiotherapy through a randomized study failed through the inability to accrue patients (5). Two randomized studies compared surgery alone versus radiotherapy alone (6,7). In 1994, Fok *et al* (6) reported a four-arm study comparing surgery alone, preoperative radiotherapy and surgery, postoperative radiotherapy and surgery, and radiotherapy alone. The study was conducted in Hong Kong and included 156 patients. Median survival for surgery versus radiotherapy was 21.6 months versus 8.2 months ($p<0.001$). Similarly, in 1999 Badwe *et al* (7) reported a randomized study comparing surgery alone versus radiotherapy alone. A total of 99 patients participated in this study. Overall survival was significantly superior in the surgery arm versus the radiotherapy arm ($p=0.002$). The generalizability of these results to contemporary surgical and radiotherapy techniques and practices and the selection factors that need to be considered when choosing between these two treatment modalities will be discussed in a separate guideline for the overall management of esophageal cancer that would be produced in due course.

Studies of the patterns of care of esophageal cancer in North America have shown an increase in the use of combined chemoradiotherapy (RTCT). Daly *et al* (8) analyzed patterns of care using the U.S. National Cancer Database and found that the treatment modality most commonly employed for esophageal cancer is combined radiotherapy and chemotherapy (30.2%), followed by surgery alone (18%). The most common chemotherapy regimen used in combination with radiation is 5-fluorouracil (5FU) and cisplatin. In the Patterns of Care Study (9), the chemotherapy agents most frequently used were 5FU (84%), cisplatin (64%), and mitomycin (9%). Youssef *et al* (10) compared management and outcome of carcinoma of the esophagus in Ontario and the United States. Controlling for age, sex, histology, and sub-site, the rate of esophagectomy was similar, but the rate of primary RT was lower in Ontario. Practice patterns for the use of RT versus combined RTCT, and the types of chemotherapy that are being used, have not been described for Ontario or Canada.

This practice guideline report addresses the question of whether the addition of chemotherapy to a primary radiotherapy approach improves patient outcomes. A separate guideline is being prepared on the use of neoadjuvant or adjuvant therapy for resectable esophageal cancer when surgery is the primary modality (PG2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*). Eventually, the Gastrointestinal Cancer Disease Site Group (DSG) will consolidate both guidelines to produce a comprehensive recommendation for patients with localized carcinoma of the esophagus who are treated with curative intent.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (11). Evidence was selected and reviewed by two members of the PGI's Gastrointestinal Cancer Disease Site Group and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on combined modality radiotherapy and chemotherapy in the non-surgical management

of localized esophageal cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

The systematic review component of this guideline report has been published as a Cochrane Review (12).

Literature Search Strategy

MEDLINE (1966 to December 2001), CANCERLIT (1983 to October 2001), and the Cochrane Library (2001, Issue 4) were searched with no language restrictions. Medical subject heading (MeSH) terms employed included "esophageal neoplasms" with subheadings "drug therapy", "radiotherapy", or "therapy". The terms used to capture randomized trials included the use of "randomized controlled trials", "controlled clinical trials", "random allocation", "exp clinical trials", and the text word "random". The proceedings of the 1999, 2000, and 2001 annual meetings of the American Society of Clinical Oncology (ASCO) and the American Society for Therapeutic Radiology and Oncology (ASTRO) were also searched. Ongoing trials were identified through the Physician Data Query (PDQ) database (http://www.cancer.gov/search/clinical_trials/).

Update

The literature search was updated on February 10, 2005 using the following databases: MEDLINE (through February week 1, 2005), EMBASE (through week 6, 2005), and the Cochrane Library's dB of Systematic Reviews (through Issue 4, 2004). Abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology through 2004 were also searched for relevant evidence. The National Cancer Institute's (NCI) clinical trials database was also searched on February 10, 2005 for listings of ongoing clinical trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials of combination chemotherapy and radiotherapy compared with radiotherapy alone in adult patients with primary esophageal carcinoma.

Exclusion Criteria

1. Esophagectomy as a planned intervention
2. Use of pure radiosensitizer (e.g. misonidazole) with radiotherapy

Study Endpoints

The primary endpoint of interest was overall survival. Data were examined for one- to five-year overall mortality rates. Secondary endpoints included local recurrence and adverse effects. While disease-specific survival and quality-of-life data would be useful endpoints to consider, they were not reported by the primary authors of the eligible trials and could not be evaluated. The data in this report are based on the intention-to-treat (ITT) principle unless data for only evaluable patients were reported and there was insufficient information to allow for an ITT analysis.

Synthesizing the Evidence

Studies of combined modality radiotherapy and chemotherapy can generally be categorized as using a **concomitant** or **sequential** approach based on the relative timing of the radiotherapy and chemotherapy, with different biological bases behind their designs. In this report, the trials that used a concomitant approach were described and analyzed separately from trials using a sequential approach. When data from trials of sequential and concomitant approaches were examined together, the pooled data were heterogeneous, suggesting that the studies are different in nature. Thus, a combined analysis of both approaches was rejected.

Data on survival and local recurrence were pooled and the results were examined for statistical heterogeneity. For each meta-analysis, data were pooled at a common time-point (e.g., mortality at one-year). The time point selected for meta-analyses must be clinically credible and relevant but not so far along the survival curve that wide confidence intervals result from fewer patients contributing to the estimate. Since time points prior to the median will generally ensure that there is sufficient data to be credible, the median survival times, weighted by the size of the treatment arms, were calculated to determine an appropriate time point for each meta-analysis. Pooling was conducted using one-year mortality data for all meta-analyses because the weighted median survival time was less than one year for both the concomitant and sequential groups (13).

The study results were pooled using Review Manager 4.0.3 (Metaview© Update Software), which is available through the Cochrane Collaboration. The random effects model was used as the more conservative estimate of effect (14). Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). An OR less than 1.0 favours the experimental treatment (i.e., RTCT) and an OR greater than 1.0 favours the control (i.e., RT alone). In addition, the absolute difference is presented as percent difference in outcome, calculated from the pooled event rates. The number of patients that need to be treated with RTCT for one additional patient to benefit (NNT) was also calculated.

Results for adverse effects were not pooled because the primary authors of eligible trials reported data on adverse effects using different scoring systems and symptom categories. The presentation of the incidence of adverse effects (as opposed to the numbers of patients affected within each toxicity grade) makes a quantitative summary statistic difficult. The results were summarized in a descriptive fashion for this review based on the incidence of grade of toxicity for acute and late adverse effects, where available across the studies, to allow for a qualitative comparison.

Data extraction was performed independently by two members of the Gastrointestinal Cancer DSG. Discrepancies were resolved through consensus.

Subgroup Analysis

It was hypothesized a priori that the use of cisplatin versus non-cisplatin chemotherapy would have an impact on the effectiveness of treatment, and a subgroup analysis was planned to

examine this hypothesis. The two most commonly employed chemotherapy regimens in Canada are 5FU/mitomycin and 5FU/cisplatin, and one of the major decisions facing clinicians is what type of chemotherapy to use if the combined modality approach is adopted. Furthermore, cisplatin-based chemotherapy has been used in combination with radiotherapy in many other disease systems resulting in significant improvement in outcome (15-20). It is, therefore, important to explore the impact of cisplatin versus non-cisplatin chemotherapy within the context of combined modality.

Potential Sources of Heterogeneity and Sensitivity Analysis

The following factors were postulated *a priori* to be potential sources of heterogeneity: study quality using scores on the Jadad scale (21) (>2 versus ≤2); dose of radiotherapy (BED[2] >60 versus BED ≤60); and type of chemotherapy (cisplatin-containing versus others). These factors were used to explore any significant heterogeneity of results across the trials. Heterogeneity of study results was assessed using a visual plot (22) and by calculating the Breslow-Day statistic using a planned cut-off for significance of $p<0.05$. The robustness of our conclusions was examined through subsequent sensitivity analyses using these factors.

IV. RESULTS

Literature Search Results

No fully published reports of meta-analyses were identified, although the pooling of data presented in this guideline report was published in abstract form in 1999 (23). This abstract will not be discussed further because the meta-analysis has been updated for this guideline report. A related study by Smith *et al* (24) was excluded due to surgery being a planned option within the study design.

Ten randomized trials of concomitant RTCT met the inclusion criteria (25-34). After a careful evaluation of the methodology, it was decided to include only eight of these trials (25-32) in the analysis. The trial by Hukku *et al* (33) was excluded because of concerns about the adequacy of the randomization procedure. Between 1990 and 1992, Kolaric *et al* reported five identical abstracts (34-38) for the same trial. This trial was excluded because there is sufficient uncertainty and absence of appropriate data for the clinical question we were trying to answer. Of the eight trials of concomitant RTCT that were included in the analysis, all but one trial (29) have been fully published. In addition to the report of long-term follow-up of the trial by the Radiation Therapy Oncology Group (RTOG) (32), five prior reports of this trial were identified and reviewed for data extraction (39-43). Five fully published, randomized trials of sequential RTCT met the inclusion criteria and were included in this review (44-48).

Update

Updating activities found an RCT by Savani and Jani reported in abstract form (1u). This trial compared RTCT to RT alone in a sample of 48 patients diagnosed with squamous cell carcinoma. There were insufficient details in the abstract regarding the intervention (dose regimen of chemotherapy and radiotherapy employed, timing of radiotherapy and chemotherapy), adequacy of the randomization process, and outcomes of interest (duration of follow up, overall survival, local recurrence rates, or late toxicities). Available study characteristics are included in Table 1-

[2]BED indicates biological effective (or equivalent) dose. To facilitate comparison across trials, radiotherapy dose was converted to biological equivalent dose using the equation $BED=nd\,(1+d/\alpha/\beta)$, where n=number of fractions, d=dose per fraction, and the assumption that $\alpha/\beta = 10$ for tumour effect. Due to the limitations of this model, no allowance can be made for time gaps in split-course treatments.

2. The investigators provided information on complete response post treatment, dysphagia relief, and acute toxicities in the abstract. The authors concluded that multimodal therapy with RTCT is a better therapeutic option, with acceptable (acute) toxicity profile and good response rate. Due to insufficient detail to permit optimal assessment of the study, the available outcome data (response rate, dysphagia relief, or acute toxicities) were NOT incorporated into the current review. Additional data from this trial will be incorporated in this review as full results become available.

Outcomes

Study Characteristics

Tables 1 and 2 outline the pertinent study characteristics and the treatment regimens. Patients with squamous cell carcinoma were included in all trials, with six trials devoted exclusively to this pathology (25,27,28,31,44,46). All of the other trials included both squamous cell carcinoma and adenocarcinomas. The extent of the primary disease was variable, with the majority of patients suffering from locally advanced disease. All trials excluded patients with distant metastases although this was done without the benefit of any abdominal imaging in all but three trials (31,32,44). It is highly probable that a substantial proportion of included patients had non-localized disease. Patients with disease spread to the supraclavicular lymph nodes were accepted in three trials (26,32,44). The presence or absence of disease spread to the mediastinal lymph nodes was not specified in any of the published eligibility criteria. Most trials used specified criteria to exclude patients in poor general condition. The chemotherapy regimens varied across the trials and included methotrexate (44), bleomycin (25-27), cisplatin (29,30), cisplatin and bleomycin (47), 5FU, mitomycin and bleomycin (28), 5FU and cisplatin (31,32,45), oral futrafur (46), and intraarterial adriamycin, 5FU and cisplatin (48). In general, the duration of follow up was short with only one- and two-year mortality data available for comparison. Table 3 provides survival data for the randomized trials. Five-year survival data were available for only three trials (28,32,44).

Table 1. Characteristics of randomized trials of combined modality radiotherapy and chemotherapy compared with radiotherapy alone.

Study (Reference)	Study Period	Number of Patients Randomized		Inclusion Criteria	Minimum Duration of Follow-up
		RT	RTCT		
Trials of Concomitant RTCT Versus RT					
Earle, 1980 (25)	1974-78	44	47	Unresectable or medically inoperable Include recurrence after radical surgery Squamous cell carcinoma	1 year
Zhang, 1984 (26)	1979	51	48	Medically inoperable Age <72 Squamous or adenocarcinoma	2 years
Andersen, 1984 (27)	1977-81	42	40	Medically inoperable T1-2N0M0 Above T5	not reported
Araujo, 1991 (28)	1982-85	31	28	Operability not stated Squamous cell carcinoma Stage II Survival >3 months	not reported
Roussel, 1994 (29) (abstract)	1983-89	111	110	Inoperable squamous cell carcinoma	4 years
Kaneta, 1997 (30)	1994-96	12	12	Resectability not stated Measurable disease Squamous cell carcinoma <79 years old Performance status 0-2	not reported
Slabber, 1998 (31)	1991-95	36	34	T3NxM0 Squamous cell carcinoma only ECOG performance status <3	3 years
Cooper/ RTOG*, 1999 (32)	1986-90	62	61	Operability not stated Squamous cell carcinoma or adenocarcinoma Karnofsky performance status ≥50	5 years
Trials of Sequential RTCT Versus RT					
Roussel, 1989 (44)	1976-82	86	84	Inoperable squamous cell carcinoma <25% weight loss	not reported
Zhou, 1991 (45)	1986-88	32	32	Early esophageal carcinoma <7.5cm	9 months
Hishikawa, 1991 (46)	1987-88	25† 8‡	24† 5‡	Operability not stated Squamous cell carcinoma <80 years old Performance status 0-3	not reported
Hatlevoll*, 1992 (47)	1983-88	51	46	Inoperable Karnofsky performance status >50	not reported
Lu, 1995 (48)	1990-92	30	30	Pathology not specified No entry criteria specified	not reported
Update					
Savani (1u)	not reported	24	24	Squamous cell carcinoma No metastases (no other criteria available)	not reported

RTCT, radiochemotherapy; RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group.
*Data available for only evaluable patients.
†Patients stratified to receive external beam radiotherapy.
‡Patients stratified to receive external beam and brachytherapy.

Table 2. Treatment regimens employed in randomized trials of combined modality radiotherapy and chemotherapy compared with radiotherapy alone.

Study (Reference)	CT Agents Regimen/Route	RT Dose Fractionation	Biological Equivalent Dose (BED)	RT Volume/Margin
Trials of Concomitant RTCT Versus RT				
Earle (25)	bleomycin IV weekly	50Gy in 5-6 weeks (in 30% of patients) 6000cGy (in 70% of patients)	60-72	3 cm margin
Zhang (26)	bleomycin IM x2-3 per week to total of 100mg	39-73 Gy in 4-7.5weeks (average 63.5Gy)	76.8	6 cm margin
Andersen (27)	bleomycin IM daily with RT, then x2 per week for 6 months	35Gy in 20 fractions, 3 week gap, 28Gy in 15 fractions (RT arm) 30Gy in 20 fractions, 3 week gap, 25Gy in 15 fractions (RTCT arm)	63.7 RTCT, 74 RT	not reported
Araujo (28)	5FU IV infusion day1-3 mitomycin day1 bleomycin IM day1,7,14,21,28	50Gy in 25 fractions	60	5 cm margin
Roussel (29) (abstract)	cisplatin 100mg/m^2 day 1,23	20Gy in 5 fractions, 15 day rest, 20Gy in 5 fractions	56	not reported
Kaneta (30)	cisplatin 5mg/m^2/day	60Gy in 30 fractions Boost: 10-12Gy in 2-6 fractions	72 (with boost 0-19)	not reported
Slabber (31)	cisplatin 15mg/ m^2/day bolus 5FU 600mg/ m^2/day infusion day1-5,29,33	20Gy in 5 fractions, 3 week rest, 20Gy in 5 fractions	56	5 cm margin
Cooper/ RTOG (32)	5FU infusion day1-4, for weeks 1,5,8,11 cisplatin weeks 1,5,8,11	Large field 30Gy in15 fractions Boost of 20Gy in 10 fractions to large field, 14Gy in 7 fractions to small tumour (RT arm) or 20Gy to tumour boost (RTCT arm)	60 RTCT, 76.8 RT	Large: SCF to esophago-gastric junction Boost: 5 cm margin
Trials of Sequential RTCT Versus RT				
Roussel (44)	methotrexate subcutaneously every 6 hours, day1-4	40.50 Gy in 18 fractions boost: 15.75 Gy in 7 fractions Gap between CT and RT: 8-12 days	68	Large: tumour and nodes Boost: tumour
Zhou (45)	cisplatin, day1-2 5FU day 3,6,10,13	65-75 Gy in 6-7 weeks Gap between CT and RT: 2-27 days	81-94	not reported
Hishikawa (46)	futrafur 600mg po at least 1 month	For external beam RT group: 60-70 Gy in 33-35 fractions For external beam and brachytherapy group: External beam: 50-60 Gy in 28-30 fractions and brachytherapy: 10-15 Gy Gap between CT and RT: 1 month	70-74 59-72*	not reported
Hatlevoll (47)	cisplatin day1-5, day 15-19 bleomycin day1-5,day 15-19	35Gy in 20 fractions, 3 week gap, 28Gy in 16 fractions Gap between CT and RT: not stated explicitly, but presumably the week after completion of CT	74	(suprasternal notch to esophago-gastric junction) Boost: 5 cm margin
Lu (48)	Intraarterial: adriamycin 60mg, 5FU 1g, cisplatin 40mg for 2 cycles, each 3-4 weeks apart	RT arm: 60-70 Gy in 30-35 fractions RTCT arm: 50 Gy in 25 fractions	72-84 60	not reported
Update				
Savani (1u)	Cisplatin + 5FU 750 mg/m^2	RT dose regimen not available Gap between CT and RT not available	not reported	not reported

RTCT, radiochemotherapy; RT, radiotherapy; CT, chemotherapy; Gy, Gray; IV, intravenously; IM, intramuscularly; 5FU, 5-Fluorouracil, and SCF, supraclavicular fossae. *BED calculation did not take into account brachytherapy dose contribution.

Mortality

For trials of concomitant RTCT, data on mortality were available at one year for seven trials (25,26,28-32). There was no statistically significant heterogeneity among the trials of concomitant RTCT when one-year mortality data was considered (p=0.49). Pooling across the seven trials involving 687 patients at one year resulted in an OR of 0.61 (95% CI, 0.44 to 0.84; p<0.00001) in favour of concomitant RTCT (Figure 1). When expressed as an absolute mortality rate, the one-year mortality rate for RTCT versus RT alone was 56% versus 67%. This is an absolute difference of 11% and a NNT of 9.

The pooled analysis of five trials involving 440 patients of sequential RTCT versus RT (44-48) revealed no significant difference in survival between the treatment groups at one year (Figure 2). There was significant heterogeneity across the trials (p=0.03), but there were too few studies to allow for a meaningful exploration of the potential sources of heterogeneity.

Subgroup analysis

It was hypothesized a priori that the use of cisplatin versus non-cisplatin chemotherapy would have an impact on the effectiveness of treatment. When only concomitant RTCT trials using cisplatin-containing chemotherapy were included (29-32), a statistically significant survival benefit was detected at one year (OR, 0.54; 95% CI, 0.36 to 0.82; p=0.003) (Figure 3).

Sensitivity analysis

Sensitivity analyses were conducted to test the robustness of the results of the pooled analyses. The two variables that were examined by additional analyses were study quality and radiation dose in combined RTCT.

The exclusion of lower quality studies and studies reported only in abstract form did not have a significant impact on the conclusion.

The radiotherapy dose fractionation employed, especially as it was used in the control arm, has important implications on whether the study was optimally designed to evaluate the use of combined concomitant RTCT as a potentially curative therapy. Sensitivity analysis using one-year mortality data (Figure 4) was performed for studies using a BED of $\geq$ 60Gy-1 and <60Gy-1. In this analysis, no statistically significant survival benefit was detected for studies using BED $\geq$ 60Gy-1 (OR, 0.76; 95% CI, 0.46 to1.25; p=0.3), and significant benefits were observed in only the two studies that employed BED of <60Gy-1 (OR, 0.54; 95% CI, 0.32 to 0.90; p=0.02). This observation infers that the survival benefit observed may be due to chemotherapy compensating for suboptimal radiotherapy dosing rather than augmenting survival beyond what optimal radiotherapy alone could provide.

Table 3. Results of randomized trials of combined modality radiotherapy and chemotherapy compared with radiotherapy alone.

Study (Reference)	Treatment Group	Number of Patients Randomized	Survival Rate (%) 1yr 2yr 3yr 4yr 5yr	Median Survival (log-rank p-value)
Trials of Concomitant RTCT Versus RT				
Earle (25)	RT RTCT	44 (37 evaluable) 47 (40 evaluable)	32 11 NR NR NR 22 9 NR NR NR	6.4 months 6.2 months NS (p-value NR)
Zhang (26)	RT RTCT	51 48	NR 20 NR NR NR NR 42 NR NR NR (p<0.05)	9 months 15 months p<0.05
Andersen (27)	RT RTCT	42 40	NR 12 NR NR NR NR 12.5 NR NR NR	NR NR
Araujo (28)	RT RTCT	31 28	55 22 11 6 6 64 38 22 16 16 (p=0.16)	15 months* 17 months* p=0.16
Roussel (29) (abstract)	RT RTCT Local recurrence RT: 73/111 RTCT: 65/110 p=0.015 time to local recurrence	111 110	31 16 NR 10 NR 47 20 NR 8 NR	7.8 months 10.5 months p=0.17
Kaneta (30)	RT RTCT	12 12	24 NR NR NR NR 40 NR NR NR NR	7 months 9 months NS (p-value NR)
Slabber (31)	RT RTCT	36 34	20 0 NR NR NR 28 0 NR NR NR	4.7 months 5.6 months p=0.42
Cooper/ RTOG (32)	RT RTCT Local recurrence RT: 42/62 RTCT: 28/61 p=NR	62 61	34 10 0 NR NR 52 36 30 30 26	9.3 months 14.1 months p<0.001
Trials of Sequential RTCT Versus RT				
Roussel (44)	RT RTCT	86 (72 evaluable) 84 (78 evaluable)	35 14 6 4 4 31 14 12 11 7	8 months 9 months p=0.81
Zhou (45)	RT RTCT	32 32	45 35 NR NR NR 77 56 NR NR NR 1 year values p<0.01 2 year values p>0.05	NR NR
Hishikawa (46)	RT RTCT	25 24	**ERT** 25 12.5 NR NR NR 20 20 NR NR NR versus **ERT + HDRIBT** 54 34 NR NR NR 60 34 NR NR NR	8.8 months 11 months NS (p-value NR)
Hatlevoll (47)	RT RTCT	51 46	29 11 6 6 6 18 5 0 NR NR p=0.1895	5.5 months 5.5 months p=0.19
Lu (48)	RT RTCT	30 30	36.7 NR NR NR NR 63.3 NR NR NR NR p<0.05	NR NR p<0.05

RT, radiotherapy, RTCT, radiotherapy plus chemotherapy; NS, not statistically significant, NR, not reported; ERT, external radiotherapy, HDRIBT, high-dose-rate intraluminal brachytherapy. *Calculated from the survival curve.

Local recurrence

Data on local recurrence were available for only three trials of concomitant RTCT (28,29,32). The trial by the RTOG (32) was the only one for which local recurrence rates for years one to three was reported. Pooling of the data detected a significant reduction in local recurrence in patients treated with concomitant RTCT compared with RT alone (OR, 0.52; 95% CI, 0.31 to 0.89; p=0.004) and no statistically significant heterogeneity (p=0.23) (Figure 5). When expressed as probabilities, the recurrence rates were 55% versus 69%, with an absolute difference of 14% and a NNT of 7.

There was also no significant heterogeneity among results for trials of sequential RTCT (p=0.26). The pooled OR was 1.05 (95% CI, 0.59 to 1.87; p=0.20), indicating no significant difference in local recurrence for sequential RTCT compared with RT alone (Figure 6).

Adverse Effects

The adverse effects experienced by patients in trials of concomitant RTCT are summarized in Table 4. No information on adverse effects was available for the trial reported by Andersen *et al* (27). In four trials, acute adverse effects were reported using a grading system (29-32) while a narrative description of the intensity of the severity was provided instead of grading toxicity in three trials (25,26,28). Earle *et al* (25) described one patient with severe nausea and vomiting, one with severe stomatitis, one with severe dermatitis requiring discontinuation of chemotherapy, and one patient with white cell counts less than $2.9X10^9/l$ in the combined modality arm. In the radiotherapy alone arm, two patients had leucopenia with white cell counts less than $2.9\ X10^9/l$. Araujo *et al* (28) described three patients with severe esophagitis in the combined modality arm and no adverse effects corresponding to grade 3-4 criteria in the radiotherapy alone arm. These descriptions of toxicity intensity correspond to grade 3-4 toxicity (according to RTOG toxicity criteria). In order to facilitate presentation of the data, they are included in Table 4 under the column for acute grade 3-4 toxicity. As grade 1-2 adverse effects were not reported consistently, only grade 3-4 and toxic deaths (acute and late) are presented for comparison.

Acute adverse effects, particularly gastrointestinal and hematological toxicities, were more frequent among patients treated with concomitant RTCT compared with RT alone (Table 4). Concomitant RTCT was associated with more grade 3-4 acute adverse effects compared with RT alone. There was no difference in late toxicity between the two treatment groups. Toxic deaths were rare. Zhang (26) reported that 3/48 patients in the RTCT arm died with extensive pulmonary infiltrate which was attributed to the combination of high dose RT and bleomycin compared to 0/51 in the radiotherapy alone arm. Slabber *et al* (31) described 2/34 versus 2/36 patients in the RTCT versus RT who died following perforation after dilatation. In the trial by the RTOG (32), there was 1/61 deaths in the RTCT arm secondary to renal and bone marrow failure compared to 0/62 in the radiotherapy alone arm.

In the two trials of sequential RTCT for which data on adverse effects were reported (44,45), no toxicity grading system for intensity of adverse effects was used (Table 5). Roussel *et al* (44) observed more adverse effects with sequential RTCT, with predominantly hematological toxicity and mucositis. In addition, there was one death with myelopathy occurring in the RT alone arm, and one from severe pancytopenia in the RTCT arm. Nausea and vomiting and hematological toxicities were more common among patients in the sequential RTCT arm of the study by Zhou (45).

Table 4. Adverse effects in trials of concomitant radiotherapy and chemotherapy.

Study (Reference)	Number of Patients Randomized		Acute Grade3-4 Toxicity		Late Grade 3-4 Toxicity		Toxic Deaths	
	RT	RTCT	RT (pts)	RTCT (pts)	RT (pts)	RTCT (pts)	RT (pts)	RTCT (pts)
Earle (25)	44	47	2	4	3	3	0	0
Zhang (26)	51	48	NR	NR	NR	NR	0	3
Araujo (28)	31	28	4	8.8	20	24	1	0
Roussel (29)	111	110	0	19	NR	NR	0	0
Kaneta (30)	12	13	0	1	NR	NR	0	0
Slabber(31)	36	34	1	6	NR	NR	2	2
RTOG (32)	62	61	1.2	6.1	14	15	0	1.22

RTCT, radiochemotherapy; RT, radiotherapy; Pts, patients; NR, not reported; RTOG, Radiation Therapy Oncology Group.

Table 5. Adverse effects in trials of sequential radiotherapy and chemotherapy.

Study (Reference)	Number of Patients Randomized		Any Toxicity		Toxic Deaths	
	RT	RTCT	RT	RTCT	RT	RTCT
Roussel (44)	84	86	Fistula 3	Mild hematological 23 Severe skin/mucositis/ esophagitis 5 Severe hepatic 1 Fistula 1	1	1
Zhou (45)	32	32	WCC <4: 2	Nausea and vomiting mild 12, 10 moderate, 8 severe WCC <4 :8 Platelet count <80: 5	0	0
Update						
Savani (1u)	24	24	Mucositis 3; vomiting 2.5; anemia 2. No grade 3-4 toxicity was reported.	Delay in treatment due to toxicity effects 3; dose reduction required 1.	0	0

RTCT, radiochemotherapy; RT, radiotherapy; WCC, white cell count.

V. INTERPRETIVE SUMMARY

Based on the pooled analyses, concomitant RTCT compared with RT alone was associated with an absolute reduction of one-year mortality from 67% to 56%, with a NNT of 9. The recurrence rate was reduced from 69% with RT alone to 55% with concomitant RTCT, with a NNT of 7. These benefits, while relatively modest, are not trivial considering the generally poor survival rates and the morbidity associated with an uncontrolled primary tumour. However, these advantages are associated with a significant increase in potentially life-threatening and severe adverse effects (grade 3-4). While quality of life was not evaluated in any of these trials, this aspect also demands consideration within the context of the magnitude of the survival advantage and expected survival rate based on disease and patient status.

An appreciation of the primary conclusions of the studies and their impact on clinical practice patterns over time would help to put the current review in perspective. All of the published studies, with the exception of Zhang (26) (which was published only in the Chinese literature, and

therefore has received very little attention), have suggested that RTCT is ineffective, until the results published by the RTOG (32). Despite the long history of negative studies, this one positive RTOG study has, for several reasons, resulted in substantial changes to clinical practice since its publication. The RTOG study supports the findings of many phase II studies suggesting a favourable outcome, but perhaps more importantly, the results are consistent with similar benefits observed in other solid tumours, such as head and neck, lung, and cervical cancer, when concomitant cisplatin was used with radical radiotherapy (15-20). In a disease where the general outcome is uniformly poor, a single positive study conducted by a large collaborative group was sufficient to motivate the adoption of this approach in standard clinical practice.

How strong is the evidence in support of combined modality? Given the methods employed to evaluate the literature, this quantitative review represents a comprehensive search of the existing data from randomized studies, and as such, represents the best available data for any evidence-based conclusions. However, three major factors will continue to limit the strength of our conclusions. First, many different types of chemotherapy regimen were tested among the studies identified. Second, long-term data are lacking for many of the included studies. Third, the sensitivity analysis raised the possibility that the observed survival benefit at one year may be explained by chemotherapy compensating for suboptimal radiotherapy doses in some studies, rather than combined chemotherapy/radiotherapy being able to improve outcome beyond what could be achieved by optimal radiotherapy alone. Despite these limitations, it is unlikely that further clinical trials using radiotherapy alone as a control arm will be undertaken to provide additional evidence to address this question, given the current practice patterns in North America.

The current review illustrates a benefit in local control and survival with the use of concomitant RTCT. This result in turn supports the common clinical practice of employing combined RTCT when offering a non-surgical approach with a curative intent for the management of esophageal cancer. In patients with favourable performance status and who have a reasonable chance of completing concomitant RTCT, this approach is a reasonable option compared with radiotherapy alone. Participation in clinical trials is strongly encouraged to further define the optimal strategy needed to minimize adverse effects and further enhance treatment outcomes within the context of combined RTCT.

There was no evidence to suggest any survival or local control benefit using sequential RTCT compared with RT alone. Given these results and the increased adverse effects associated with sequential RTCT, this approach should not be recommended in standard practice.

VI. ONGOING TRIALS

No ongoing trials were found that addressed the guideline question and met the inclusion criteria for this review of the evidence. Clinical trials designed to reduce toxicity and further augment the outcome of this approach are ongoing, and participation in these trials should be encouraged.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Gastrointestinal Cancer DSG readily agreed upon and approved the contents of the practice guideline report. The committee felt, however, that it was important to highlight the following issues.

The meta-analysis of survival benefit was based on one-year data only; therefore, caution must be used when interpreting the results, especially when long-term survival benefit is considered.

The Gastrointestinal Cancer DSG members debated how to address the issue of what type of chemotherapy to recommend in the context of a combined radiotherapy and chemotherapy approach. The current review was undertaken to address the general question of whether a combined approach is superior to radiotherapy alone and, therefore, was not designed to answer the question of what specific type of chemotherapy-radiotherapy regimen is superior to others. To address the latter question, we would need to review randomized studies comparing a standard type of combined radiotherapy and chemotherapy versus an experimental one, but these studies are not available. In the current review, it was hypothesized that whether or not cisplatin-based chemotherapy was used would have an impact on the conclusion of the review, and the subgroup analysis in fact did support this. The current clinical practice in North America in this area has been heavily shaped by the results of the RTOG study (32). There has been a substantial increase in the use of combined radiotherapy and chemotherapy in recent years (8), and when it is used, 5FU and cisplatin are the chemotherapy agents most commonly employed (9). The DSG felt that given the results of the meta-analysis and the current practice pattern, the use of a cisplatin-containing regimen should be the treatment of choice when concomitant radiotherapy and chemotherapy is used. For patients with poor performance status, radiotherapy alone or optimal palliative therapy should be considered.

The DSG also felt that it is important to point out the significant risk of toxicity associated with concomitant radiotherapy and chemotherapy. This fact may indeed outweigh the potential benefits in survival and local control, depending on the patient's general condition. The decision to adopt a combined radiotherapy and chemotherapy approach over radiotherapy alone for the curative management of carcinoma of the esophagus should be undertaken only after due consideration of these factors and in consultation with the patient.

The group also felt it should be made clear that there are no randomized trials of chemoradiation alone versus surgery alone as the primary modality for patients with curable esophageal cancer who are suitable for both (surgical and non-surgical) approaches.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Recommendations

Based on the evidence described in the original report above[3], the Gastrointestinal Cancer DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with localized carcinoma of the esophagus and good performance status who are considering a non-surgical approach and for whom combined radiotherapy and chemotherapy can be tolerated in the judgment of the treating oncologist.

Draft Recommendations

- Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice pattern and the currently available research evidence, the use of a cisplatin-based chemotherapy regimen is recommended when concomitant radiotherapy and chemotherapy is used.

[3] The two randomized trials of surgery alone versus radiotherapy alone (6,7) had not been identified when the qualifying statements were drafted.

- Patients should be aware of the increased acute toxicity associated with this approach. The decision to use concomitant radiotherapy and chemotherapy should only be made after careful consideration of the potential risks, benefits and the patient's general condition.
- Sequential radiotherapy and chemotherapy should not be recommended as standard practice.

Qualifying Statements

- Localized esophageal cancer has been managed surgically or with radiotherapy. There are no randomized trials comparing these treatments, so it is unclear whether a surgical or a non-surgical approach is superior in patients who are suitable for both approaches.

Related Guideline

Practice Guideline Initiative's Practice Guideline #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.

Practitioner Feedback

Based on the evidence contained in the original report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 163 practitioners in Ontario (28 medical oncologists, 21 radiation oncologists, 111 surgeons and three gastroenterologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above 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.

Results

Key results of the practitioner feedback survey are summarized in Table 6. Seventy-nine surveys (53%) were returned. Twenty-nine respondents (37%) (10 medical oncologists, seven radiation oncologists, and 12 surgeons) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey.

Table 6. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	27 (93%)	2 (7%)	0
There is a need for a clinical practice guideline on this topic.	25 (96%)	4 (14%)	0
The literature search is relevant and complete.	25 (86%)	2 (7%)	2 (7%)
The results of the trials described in the report are interpreted according to my understanding of the data.	27 (93%)	1 (3%)	1 (3%)
The draft recommendations in this report are clear.	27 (93%)	1 (3%)	1 (3%)
I agree with the draft recommendations as stated.	27 (93%)	1 (3%)	1 (3%)
This report should be approved as a practice guideline.	21 (72%)	5 (17%)	1 (3%)

If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	21 (72%)	7 (24%)	0

*Percentages may not total 100% due to missing data.

Summary of Written Comments

Eight respondents (28%) provided written comments. Five of the eight respondents expressed concern that the recommendation for cisplatin-based chemotherapy versus non-cisplatin-based chemotherapy goes beyond that suggested by the available evidence. A medical oncologist who disagreed with the recommendations indicated that it would be imprudent to advise concomitant radiotherapy and cisplatin-based chemotherapy for all patients until it is determined that patients with adenocarcinoma do better with radiotherapy plus cisplatin-based chemotherapy and patients with squamous cell carcinoma do better with COP (cyclophosphamide, vincristine, prednisone). This practitioner also questioned the use of odds ratios rather than absolute risk reduction and number needed to treat. Another respondent requested an algorithm to help in deciding between surgical and non-surgical treatment. The same respondent commented on the limited discussion on quality of life. One respondent wondered why a European Cooperative Oncology Group (ECOG) study of chemoradiation was not included, although this respondent also acknowledged that surgery was a planned intervention for some patients in this ECOG study.

Modifications/Actions

The Gastrointestinal Cancer DSG acknowledged the comments from the practitioner feedback survey that highlighted the limitations of the evidence in support of a cisplatin-containing regimen. These comments were forthcoming despite the fact that the limitations of the data were already discussed in the interpretive summary in the original draft. The DSG, therefore, felt it was appropriate to reword the recommendation to read "a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used." Instead of the original wording of "a cisplatin-based chemotherapy regimen is recommended when concomitant radiotherapy and chemotherapy is used."

The utility of other novel regimens will be incorporated into the guideline report through our guideline update process when relevant studies are completed and reported.

Two respondents felt that the literature identified was incomplete, although only one additional reference was cited, i.e. the ECOG study reported by Smith et al (24). This study did not satisfy our inclusion criteria because surgery was an optional but planned intervention.

Practice Guidelines Coordinating Committee Approval Process

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

One member thought that the first bullet under key evidence should end with, "*at conventional radiation dose fractionation schedules*", or "*at the doses and fractionation of radiation used in the control arms of trials*" because increasing the radiation dose or fractionation schedule could achieve improved results (but which would also increase radiation toxicity). For this reason, the same member thought there should have been an exclusion criterion for trials that used inadequate doses of radiotherapy because they give a false impression of the value of the experimental arm.

Another member stated that there should be a recommendation regarding placing patients on trials to better define concurrent chemoradiotherapy combinations that will improve outcomes with less toxicity, as this item appeared in the guideline text.

Modifications/Actions

1. Sensitivity analysis using one-year mortality data (Figure 4) was performed for studies using a BED of ≥ 60Gy-1 and <60Gy-1. In this analysis, no statistically significant survival benefit was detected for studies using BED ≥ 60Gy-1 (OR, 0.76; 95% CI, 0.46 to1.25; p=0.3); and significant benefits were observed in only the two studies that employed BED of <60Gy-1 (OR, 0.54; 95% CI, 0.32 to 0.90; p=0.02). This observation infers that the survival benefit observed may be due to chemotherapy compensating for suboptimal radiotherapy dosing rather than augmenting survival beyond what optimal radiotherapy alone could provide. Although the meta-analysis detected an outcome that was not as strong as expected, supporting the use of combined RTCT in non-surgical therapy for esophageal cancer is still a reasonable recommendation.
2. A bullet providing suggestions for future clinical trials was added to the recommendations.
3. All necessary editing changes were also made.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

Recommendations

- Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice pattern and the currently available research evidence, a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used.
- Patients should be made aware of the increased acute toxicity associated with this approach. The decision to use concomitant radiotherapy and chemotherapy should only be made after careful consideration of the potential risks, benefits, and the patient's general condition.
- Sequential radiotherapy and chemotherapy is not recommended as standard practice.
- Future clinical trials to better define the optimal chemoradiotherapy combination that would improve outcomes while limiting toxicities are strongly encouraged.

IX. 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 localized (T1-3, small volume N1, M0) carcinoma of the esophagus and good performance status who are considering a non-surgical approach and for whom combined radiotherapy and chemotherapy can be tolerated in the judgment of the treating oncologist.

Recommendations

- Concomitant radiotherapy and chemotherapy is recommended over radiotherapy alone. Based on considerations of the current clinical practice pattern and the currently available research evidence, a cisplatin-based chemotherapy regimen is a reasonable chemotherapy regimen to use when concomitant radiotherapy and chemotherapy is used.
- Patients should be made aware of the increased acute toxicity associated with this approach. The decision to use concomitant radiotherapy and chemotherapy should only be made after careful consideration of the potential risks, benefits, and the patient's general condition.
- Sequential radiotherapy and chemotherapy is not recommended as standard practice.
- Future clinical trials to better define the optimal chemoradiotherapy combination that would improve outcomes while limiting toxicities are strongly encouraged.

Related Guidelines

Practice Guideline Initiative's Practice Guideline #2-11: *Neoadjuvant or Adjuvant Therapy for Resectable Esophageal Cancer*.

X. JOURNAL REFERENCE

Wong RKS, Malthaner RA, Zuraw L, Rumble RB, and 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. *Int J Radiat Oncol Biol Phys* 2003; 55(4): 930-42.

XI. ACKNOWLEDGEMENTS

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For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO Web site at www.cancercare.on.ca/.

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Update

This section includes all references obtained from the review and updating activities.

1u. Savani B and Jani CR. Randomized trial of neo-adjuvant chemotherapy followed by radiotherapy vs radiotherapy alone in squamous cell carcinoma esophagus [abstract]. *Proc Annu Meet Am Soc Clin Oncol* 2003;354 Abstract 1423

Figure 1. Pooling of 1-year mortality data from trials of concomitant RTCT versus RT.

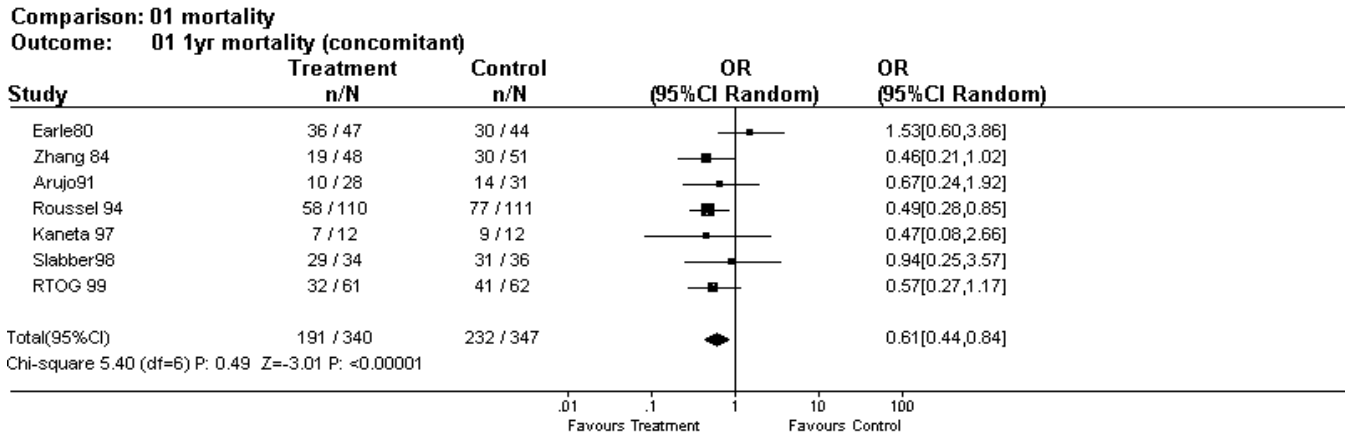


Figure 2. Pooling of 1-year mortality data from trials of sequential RTCT versus RT.

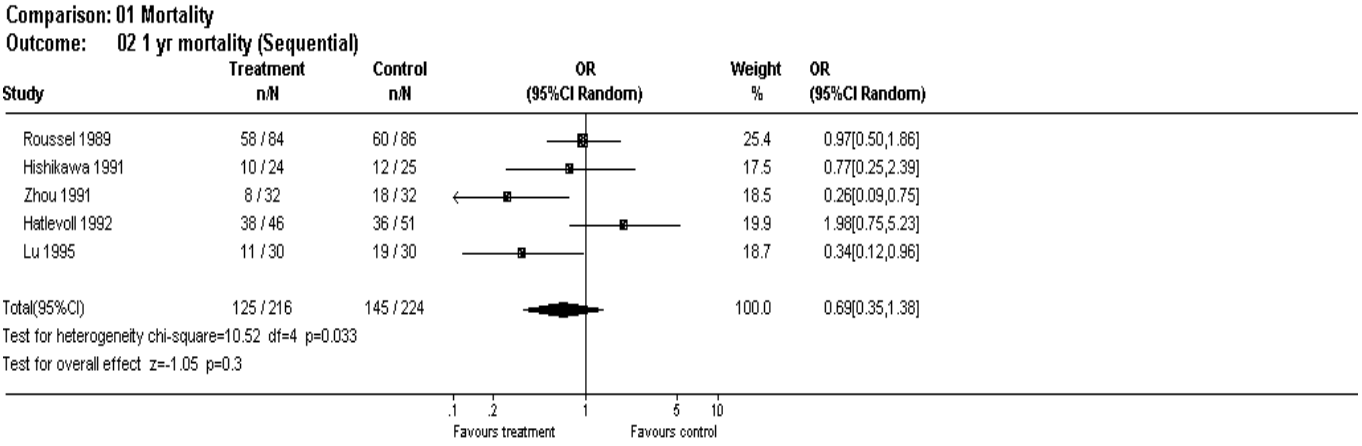


Figure 3. Subgroup analysis: cisplatin-containing studies only.

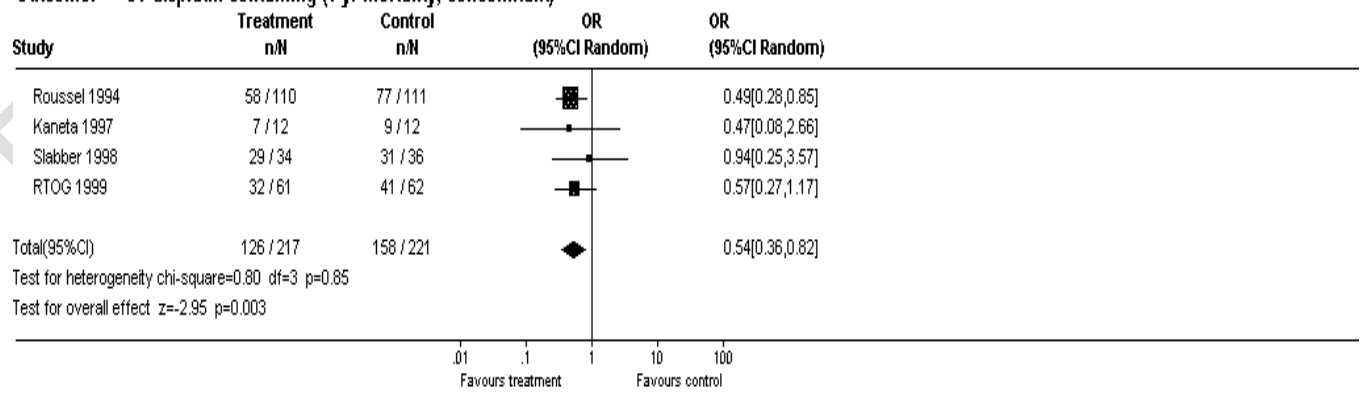


Figure 4. Sensitivity analysis results (BED <60Gy-1 versus ≥60Gy-1).

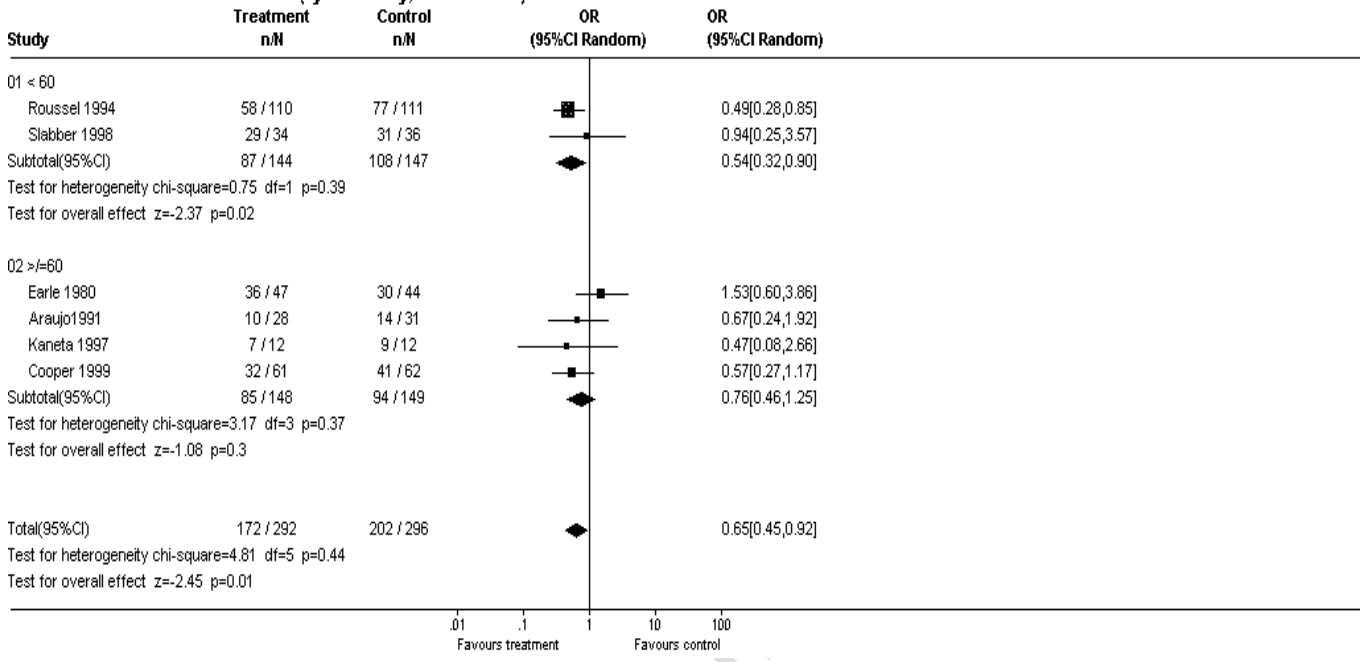
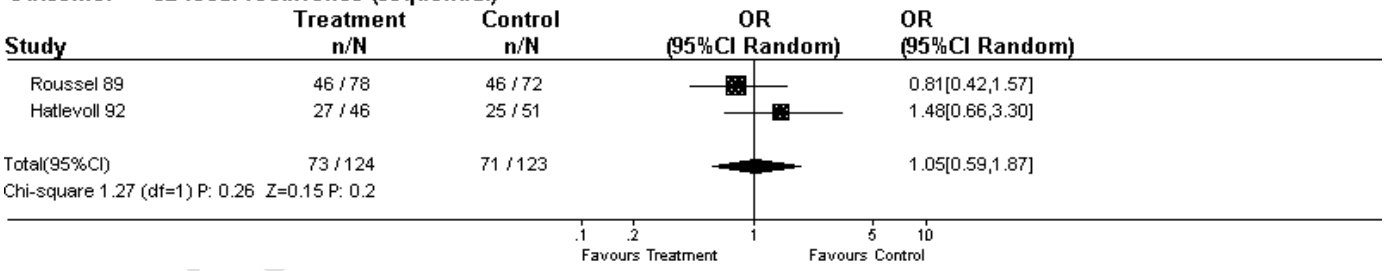


Figure 6. Trials of sequential RTCT versus RT.



EBS 2-12 Document Assessment and Review Tool.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

DOCUMENT ASSESSMENT AND REVIEW TOOL

Number and title of document under review	UPG #2-12 Combined Modality Radiotherapy and Chemotherapy in the Non-surgical Management of Localized Carcinoma of the Esophagus
Date of current version	February 10, 2005
Clinical reviewer	Dr. Rebecca Wong
Research coordinator	Rovena Tey
Date initiated	December 3, 2009
Date and final results / outcomes	**September 29, 2010 (ENDORSED)**
Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.	
1. Is there still a need for a guideline covering one or more of the topics in this document **as is**? Answer Yes or No, and explain if necessary:	1. YES If No, then the document should be **ARCHIVED**1 with no further action; **go to 11**. If Yes, then **go to 2**.
2. Are all the current recommendations based on the current questions **definitive**[*] or **sufficient**[§], and have less than **5 years elapsed** since the latest search? Answer Yes or No, and explain if necessary:	2. NO • Radiation and chemotherapy are standard therapies now • Literature search in February 2005 turned up no new studies • However, it would be useful to conduct a literature search now to see if any new studies show up If Yes, the document can be **ENDORSED**2 with no further action; **go to 11**. If No, **go to 3**.
3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:	3. NO • It would be surprising for an updated literature search to turn up contradictory evidence If Yes, the document should be taken off the Web site as soon as possible. A **WARNING**[¶] should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, g**o to 4**.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:	4. YES • There is a designated research co-ordinator at the PEBC to carry out the literature search. If No, a **DEFERRAL**[3] should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go **to 5**.
5a. List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered.	
• The current guideline question is still relevant – no changes to the Q **Question:** Does combined modality radiotherapy and chemotherapy improve survival compared with radiotherapy alone in	

patients with localized carcinoma of the esophagus for whom a non-surgical approach is used?

Target Population:
These recommendations apply to adult patients with localized (T1-3, small volume N1, M0) carcinoma of the esophagus and good performance status who are considering a non-surgical approach and for whom combined radiotherapy and chemotherapy can be tolerated in the judgment of the treating oncologist.

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

- Both phase 2 and 3 RCTs are of interest.
- No changes to the inclusion or exclusion criteria, or study endpoints

Inclusion Criteria:
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials of combination chemotherapy and radiotherapy compared with radiotherapy alone in adult patients with primary esophageal carcinoma.

Exclusion Criteria:
1. Esophagectomy as a planned intervention
2. Use of pure radiosensitizer (e.g., misonidazole) with radiotherapy

Study Endpoints:
The primary endpoint of interest was overall survival. Data were examined for one- to five-year overall mortality rates. Secondary endpoints included local recurrence and adverse effects. While disease-specific survival and quality-of-life data would be useful endpoints to consider, they were not reported by the primary authors of the eligible trials and could not be evaluated. The data in this report are based on the intention-to-treat (ITT) principle unless data for only evaluable patients were reported and there was insufficient information to allow for an ITT analysis.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials of combination chemotherapy and radiotherapy compared with radiotherapy alone in adult patients with primary esophageal carcinoma.

Exclusion Criteria:
1. Esophagectomy as a planned intervention
2. Use of pure radiosensitizer (e.g. misonidazole) with radiotherapy

Search Period:
- Medline + Embase (Feb 2005 to 23 Jul 2010)
- ASCO (2005 to 2010)
- ASTRO (2005 to 2009)

Brief Summary/Discussion of New Evidence:
Of 172 total hits from Medline + Embase; 801 abstracts from ASCO and 167 hits from ASTRO conference abstract

searches, 1 conference abstract met selection criteria of a RCT comparing chemo-RT vs. RT alone.

Interventions	Population	Outcomes	Brief results	Reference
5FU + cisplatin + split-course RT vs. continuous RT	Locoregional advanced unresectable esophageal cancer	OS (2y, 5y, 10y), median survival, adverse events	For, chemo RT vs. RT • 2y OS = 32% vs. 22% • 5y OS = 24% vs. 14% • 10y OS = 7.3% vs. 1.9% • median survival = 15 mo vs. 12 o Adverse events • Chemo RT = hematological, nausea, alopecia • RT = esophagitis, pain	Zupanc D, 2007 [***abstract***]

FU = fluorouracil; mo = month; OS = overall survival; RT = radiotherapy; vs.= versus; y = year

New Reference Identified:

Zupanc D, Roth A, Kolaric K, and Tometic Z. (2007). A randomized clinical study of chemoradiotherapy versus radiotherapy in locoregional advanced unresectable esophageal cancer. J Clin Oncol – ASCO Annual Meeting Proceedings Part I. 25;18S: 4565.

Literature Search Strategy:

Medline

1. meta-Analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5. (systematic adj (review$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or

case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. esophageal neoplasms/
39. (esophageal and (neoplasm? or cancer? or carcinoma?)).tw.
40. 38 or 39
41. chemotherapy, adjuvant/
42. radiotherapy, adjuvant/
43. (preoperative or neoadjuvant).tw.
44. 43 and chemotherapy.tw.
45. 43 and (radiotherapy or radiation therapy or irradiation).tw.
46. immunotherapy.tw.
47. (chemoradiotherapy or chemoradiation).tw.
48. hyperthermia.tw.
49. exp immunotherapy/
50. 41 or 42 or 44 or 45 or 46 or 47 or 48 or 49
51. 40 and 50
52. 37 and 51
53. (200502$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed.
54. 52 and 53

Embase

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinic$ adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. esophageal neoplasms/
34. (esophageal and (neoplasm? or cancer? or carcinoma?)).tw.
35. 33 or 34

36. chemotherapy, adjuvant/
37. radiotherapy, adjuvant/
38. (preoperative or neoadjuvant).tw.
39. 38 and chemotherapy.tw.
40. 38 and (radiotherapy or radiation therapy or irradiation).tw.
41. immunotherapy.tw.
42. (chemoradiotherapy or chemoradiation).tw.
43. hyperthermia.tw.
44. exp immunotherapy/
45. 36 or 37 or 39 or 40 or 41 or 42 or 43 or 44
46. 35 and 45
47. 32 and 46
48. (200506$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ew.
49. 47 and 48

ASCO – manually searched www.asco.org from all abstracts in the section: Gastrointestinal (noncolorectal) cancer – esophageal, gastric, or small bowel

ASTRO – searched supplement issues of conference proceedings from www.redjournal.org with title keyword esophag*

Go to 6.

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?	6. NO If Yes, then the document should be **ARCHIVED** with no further action; **go to 11**. If No, **go to 7**.
7. On initial review, does the newly identified evidence support the **existing recommendations**? Do the current recommendations **cover all relevant subjects** addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:	7. YES • The new evidence (1 conference abstract) supports existing recommendations • We also don't expect that stronger evidence will be published in the near future that would change the current recommendations • Therefore, guideline 2-12 can be **ENDORSED**. If Yes, the document can be **ENDORSED**. If No, **go to 8**.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:	8. not applicable If Yes, a **WARNING** note will be placed on the web site. If No, **go to 9**.
9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	9. not applicable If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, **go to 10.**
10. An update should be initiated as soon as possible. List the expected date of completion of the update:	10. not applicable An **UPDATE**[4] will be posted on the Web site, indicating an update is in progress.

11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.	
DSG Approval Date:	**September 29, 2010**

DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

STEPS **Outcomes** **Action**

STEP 1: Initiation of the Document Assessment & Review process

RC emails DSG reviewer(s) the protocol

STEP 2: First teleconference to determine:
- **the clinical relevance of the guideline,**
- **if a new literature search is needed, and**
- **if Yes, the search criteria.**

Discuss questions **#1-5**

#1. Is there still a **NEED** for a guideline covering one or more of the **topics** in this document?

No → **Archive**[1]

Yes

#2. Are all the current recommendations based on the current questions definitive* or sufficient[§], and have less than 5 years elapsed since the latest search?

Yes to all → **Endorse**[2]

No

#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?

Yes ⇢ **Warning**[¶]

No

#4. Do current resources allow for an updated literature search to be conducted at this time?

No → **Deferral**[3]

Yes

#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

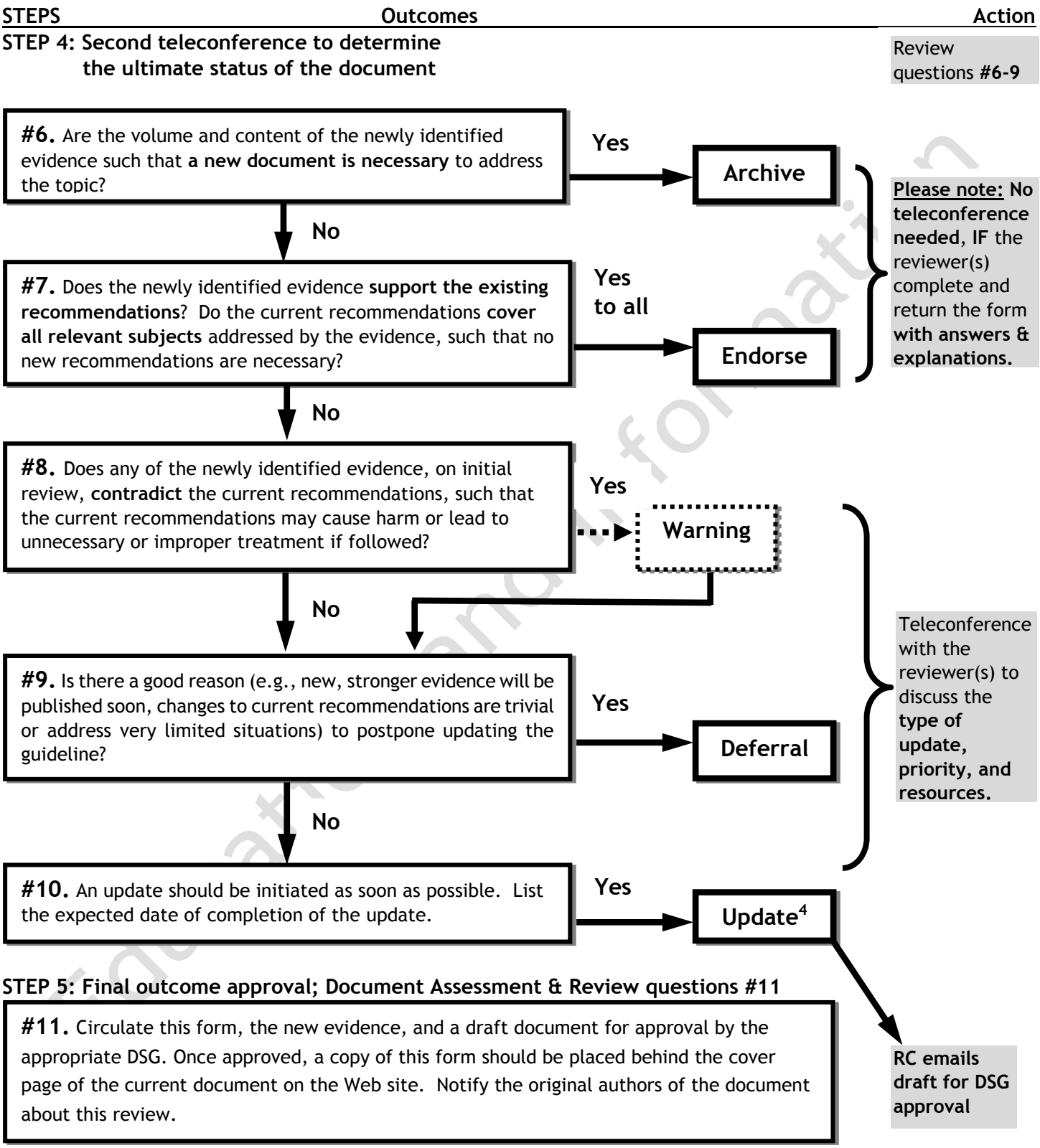
⇢ **New search** ⇢ **RC conducts new search**

Please note: **No teleconference needed, IF** the answers lead to one of these outcomes, **PLUS** the reviewer(s) complete & return the form **with the answers & explanations.**

Teleconference with the reviewer(s) will focus the discussion on **#5**: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria

STEP 3: A new literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date

FLOW CHART (cont.)



DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*__DEFINITIVE RECOMMENDATIONS__ – Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§__SUFFICIENT RECOMMENDATIONS__ – Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶__WARNING__ – A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and **each page is watermarked** with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. **UPDATE –** An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.