

Review: Neoadjuvant chemoradiotherapy and chemotherapy improve survival in operable esophageal cancer

Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol*. 2007;8:226-34.

Clinical impact ratings: Gastroenterology ★★★★★☆☆☆ Oncology ★★★★★★★★

QUESTION

In patients with operable esophageal cancer, does neoadjuvant chemoradiotherapy or chemotherapy given before surgery increase survival?

METHODS

Data sources: Reference lists of previous systematic reviews, MEDLINE, EMBASE/Excerpta Medica, Cancerlit, and lists of conference abstracts (1980 to 2006).

Study selection and assessment: English-language randomized controlled trials (RCTs) that compared neoadjuvant chemoradiotherapy or chemotherapy followed by surgery with surgery alone in the initial management of operable esophageal cancer and did intention-to-treat analysis. 10 RCTs ($n = 1209$, median age 62 y, range 28 to 83 y) of neoadjuvant chemoradiotherapy and 8 RCTs ($n = 1724$, median age 63 y, range 30 to 84 y) of neoadjuvant chemotherapy met the selection criteria.

Outcomes: Overall survival.

MAIN RESULTS

Chemoradiotherapy improved overall survival, but the effect of chemotherapy was smaller and of borderline statistical significance (Table). Chemoradiotherapy was effective for patients with squamous cell carcinoma (SCC) (hazard ratio [HR] for death 0.84, 95% CI 0.71 to 0.99) and with adenocarcinoma (HR 0.75, CI 0.59 to 0.95). In patients with SCC, concurrent chemoradiotherapy improved survival (HR 0.76, CI 0.59 to 0.98) but sequential chemoradiotherapy did not (HR 0.90, CI 0.72 to 1.03). Neoadjuvant chemotherapy improved survival for adenocarcinoma (HR 0.78, CI 0.64 to 0.95)

but not for SCC (HR 0.88, 0.75 to 1.03) or mixed tumors (HR 1.07, CI 0.87 to 1.32).

CONCLUSION

Neoadjuvant chemoradiotherapy and chemotherapy improve survival in patients with operable esophageal cancer.

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Overall survival with neoadjuvant therapy plus surgery vs surgery alone for esophageal cancer at 2 years (median follow-up 4 years)*

Type of neoadjuvant therapy	Number of trials (n)	Neoadjuvant therapy plus surgery	Surgery alone	RBI (95% CI)	NNT (CI)
Chemoradiotherapy	10 (1209)	39%	33%	18% (6 to 32)	17 (10 to 48)
Chemotherapy	8 (1724)	36%	33%	8.8% (0 to 18)	Not significant

*Abbreviations defined in Glossary. Neoadjuvant therapy survival rates, RBI, NNT, and CI calculated from hazard ratios in article.

COMMENTARY

Although previous meta-analyses have suggested survival benefits with neoadjuvant concurrent chemoradiation for esophageal cancer, its role is still debated because of the heterogeneity of radiation doses and surgical results in randomized trials.

Gebski and colleagues conducted a meta-analysis of 18 randomized trials that compared neoadjuvant therapy with surgery alone. This review, which is the most comprehensive to date, included individual patient data from 2 trials and unpublished results. The findings of the meta-analysis are statistically robust and indicate that neoadjuvant chemoradiotherapy and, to a lesser degree, neoadjuvant chemotherapy lead to improved survival, particularly in patients with adenocarcinoma. However, the authors underscored the survival benefit shown by adjuvant chemoradiotherapy in gastroesophageal junction cancer (1).

Modern staging methods, including positron emission tomography and endoscopic ultrasonography, improve patient selection for neoadjuvant protocols. Advanced radiation technologies and novel chemotherapeutic agents have better outcomes than those reported by the older

studies included in this meta-analysis. Therefore, the true benefit of neoadjuvant chemoradiotherapy may be underestimated.

Neoadjuvant chemoradiotherapy should now be regarded as the treatment of choice for esophageal adenocarcinoma. Future trials should incorporate targeted agents based on tumor genetic profiles into neoadjuvant protocols.

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Reference

1. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-30.