

# Perioperative chemotherapy improved survival in resectable adenocarcinoma of the stomach or lower esophagus

Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355:11-20.

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

## QUESTION

In patients with resectable gastroesophageal adenocarcinoma, is surgery plus perioperative chemotherapy more effective than surgery alone for improving overall survival?

## METHODS

**Design:** Randomized controlled trial.

**Allocation:** Concealed.\*

**Blinding:** Unblinded.\*

**Follow-up period:** Median 4 years.

**Setting:** 56 centers in the United Kingdom, the Netherlands, New Zealand, Germany, Singapore, and Brazil.

**Patients:** 503 patients 23 to 85 years of age (median age 62 y, 79% men) with adenocarcinoma of the stomach, lower esophagus, or gastroesophageal junction that penetrated the submucosa, but without evidence of distant metastases or inoperable local disease.

**Intervention:** Surgery alone ( $n = 253$ ) or surgery plus perioperative chemotherapy

( $n = 250$ ) with epirubicin, 50 mg/m<sup>2</sup> on day 1; cisplatin, 60 mg/m<sup>2</sup> on day 1; and fluorouracil, 200 mg/m<sup>2</sup> daily by continuous intravenous infusion for 21 days, given for 3 cycles before surgery and 3 cycles after surgery.

**Outcomes:** Overall survival. Secondary outcomes included surgical and pathologic assessments of tumor size and stage, postoperative complications, and mortality within 30 days.

**Patient follow-up:** 100% (intention-to-treat analysis).

## MAIN RESULTS

Overall survival was longer in the perioperative chemotherapy group than in the surgery group (hazard ratio [HR] for death 0.75, 95% CI 0.60 to 0.93, 5-year survival rates 36% vs 23%, absolute benefit increase 13%, number needed to treat 8). Preoperative chemotherapy resulted in resected tumors

that were smaller (median maximum diameter 3 cm vs 5 cm,  $P < 0.001$ ) and less extensive (T1 or T2 in 52% vs 37%,  $P = 0.002$ ), but it did not affect the rates of postoperative complications or mortality within 30 days.

## CONCLUSION

In patients with resectable gastroesophageal adenocarcinoma, surgery plus perioperative chemotherapy was more effective than surgery alone.

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\*See Glossary.

## COMMENTARY

In the management of patients with resectable cancers, increasing evidence exists that preoperative chemotherapy and radiation therapy may be equally effective and better tolerated than similar therapy delivered after surgery. The results with perioperative chemotherapy reported by Cunningham and colleagues support this concept in the management of patients with potentially resectable adenocarcinoma of the stomach or gastroesophageal junction. In an era when the correct surgical procedure for such patients remains controversial (1), the 5-year survival rate in patients treated with chemotherapy was 36% compared with 23% in patients treated with surgical resection alone.

Despite these positive results, only 55% of patients treated with preoperative chemotherapy began postoperative chemotherapy, and only 42% of patients assigned to chemotherapy completed the whole protocol. These data raise many questions, including whether postoperative chemotherapy is necessary and whether the magnitude of the benefit might be greater if a higher proportion of patients could have completed all assigned chemotherapy. It also points to the need to develop more effective, less toxic therapies that can be delivered to most patients.

Macdonald and colleagues (2) reported that the addition of a complex postoperative regimen of chemoradiation with 5-fluorouracil and folinic acid, compared with surgery alone, improved 3-year survival rates to a similar extent for patients with adenocarcinoma of the stomach or gastroesophageal junction (50% vs 41%,  $P = 0.005$ ). Comparison of these 2 trials cannot tell us which regimen is better. Improvements in survival were substantial with either perioperative chemotherapy or postoperative chemoradiation. Both approaches can be considered a standard of care for patients with operable cancers of the stomach or gastroesophageal junction.

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## References

- McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. *Cochrane Database Syst Rev.* 2004;CD001964.
- 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.