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BEST EVIDENCE TOPIC

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Can definitive chemoradiotherapy be an alternative to surgery for early-stage oesophageal cancer?

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Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: Can definitive chemoradiotherapy (CRT) be an alternative to surgery for early-stage oesophageal cancer? A total of 622 papers were found using the reported search, of which 5 cohort studies represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Three cohort studies with very limited sample size reported that definitive CRT yielded comparable overall survival to surgery, whereas the other 2 studies with large sample size reported that definitive CRT yielded worse survival than surgery. Two of the cohort studies also reported that definitive CRT was associated with significantly higher rates of recurrence than surgery. The available evidence, while both scarce and of poor quality, suggests that definitive CRT for early-stage oesophageal cancer resulted in worse overall survival and more recurrence when compared to surgery. Therefore, we would recommend that surgery still remains the standard treatment for patients with early-stage oesophageal cancer, whereas definitive CRT could be an alternative to surgery for patients unfit for surgery, although with slightly inferior outcomes.

Keywords: Oesophageal cancer • Early stage • Definitive chemoradiotherapy • Surgery • Comparison

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients with early-stage oesophageal cancer] can [definitive chemoradiotherapy (CRT)] result in outcomes comparable with surgery, such as [survival and recurrence]?

CLINICAL SCENARIO

An 80-year-old male patient with clinical Stage I oesophageal cancer was admitted for treatment. Therapeutic strategies were discussed in the multidisciplinary meeting, and the consensus was for surgical resection. However, one of your colleagues suggested that definitive CRT as a less invasive treatment could be an alternative to surgery, especially in early-stage oesophageal cancer. You resolve to check the literature for yourself.

SEARCH STRATEGY

We searched MEDLINE using the PubMed interface from 1950 to January 2018 with the search terms: ((((((((((esophageal[Title/Abstract]) OR esophageal[Title/Abstract]) OR esophagus[Title/Abstract]) OR esophagus[Title/Abstract])) AND ((((cancer[Title/Abstract]) OR carcinoma[Title/Abstract]) OR tumor[Title/Abstract]) OR neoplasm[Title/Abstract])) AND (((((chemoradiotherapy[Title/Abstract]) OR chemotherapy[Title/Abstract]) OR radiotherapy[Title/Abstract]) OR radiation[Title/Abstract]) OR radiochemotherapy[Title/Abstract])) AND ((((surgery[Title/Abstract]) OR surgical[Transliterated Title]) OR esophagectomy[Title/Abstract]) OR oesophagectomy[Title/Abstract])) AND ((early[Title/Abstract]) OR stage I[Title/Abstract]))).

SEARCH OUTCOME

A total of 622 papers were found using the reported search from MEDLINE. From these, after exclusion of irrelevant studies and those reporting specifically on early-stage oesophageal cancer, only 5 papers were finally identified that provided the best evidence to answer the question. These are presented in Table 1.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Yamamoto *et al.* (2011), Am J Gastroenterol, Japan [2] Cohort study (level 3)	A total of 170 patients with clinical Stage I oesophageal squamous cell carcinoma were included for analysis (definitive CRT group: 54 patients; surgery group: 116 patients) Treatment selection: no definitive criteria for selecting CRT or surgery in each patient CRT: cisplatin and fluorouracil-based chemotherapy + a total dose of 60 Gy in 30 fractions Surgery: oesophagectomy with 2- or 3-field lymphadenectomy via right thoracotomy	Median follow-up time 1-Year OS rates 3-Year OS rates 1-Year progression-free survival rates 3-Year progression-free survival rates	CRT group: 30 months; surgery group: 67 months ($P < 0.001$) CRT group: 98.1%; surgery group: 97.4% CRT group: 88.7%; surgery group: 85.5% ($P = 0.78$) CRT group: 84.6%; surgery group: 93.9% CRT group: 70.1%; surgery group: 81.9% ($P = 0.04$)	Patients in the CRT group were older and had larger lesions than those in the surgery group
Reid *et al.* (2012), Clin Oncol (R Coll Radiol), UK [3] Cohort study (level 3)	A total of 32 patients with clinical Stage I oesophageal cancer were included for analysis (definitive CRT group: 10 patients; surgery group: 22 patients) Treatment selection: patients deemed unsuitable for surgery on grounds of comorbidities and/or performance status, loco-regional disease considered too extensive for curative resection or personal choice received CRT CRT: cisplatin and fluorouracil-based chemotherapy + a total dose of 50 Gy in 25 fractions Surgery: oesophagectomy with or without neoadjuvant therapy	Median follow-up time Median disease-free survival 2-Year disease-free survival rate Median OS 2-Year OS rate	23 months for all those patients CRT group: 59 months; surgery group: not available CRT group: 68.6%; surgery group: 85.6% ($P = 0.069$) CRT group: 68 months; surgery group: not available CRT group: 68.6%; surgery group: 85.6% ($P = 0.236$)	Baseline characteristics in both groups were not available. This study had a small sample size
Park *et al.* (2014), Cancer Chemother Pharmacol, Korea [4] Cohort study (level 3)	A total of 284 patients with clinical T1N0M0 oesophageal cancer were included for analysis (definitive CRT group: 20 patients; surgery group: 264 patients) Treatment selection: most patients in the CRT group were medically unfit for surgery or declined the radical oesophagectomy CRT: cisplatin plus capecitabine or fluorouracil + a total dose of 54 Gy in 27 fractions Surgery: Ivor Lewis, McKeown or transhiatal oesophagectomy with 2- or 3-field lymphadenectomy	Median follow-up time 3-Year time-to-recurrence rate 5-Year time-to-recurrence rate 3-Year OS rate 5-Year OS rate	CRT group: 51.1 months; surgery group: 49.0 months CRT group: 82.7%; surgery group: 84.5% CRT group: 82.7%; surgery group: 80.7% ($P = 0.831$) CRT group: 76.8%; surgery group: 86.8% CRT group: 58.5%; surgery group: 73.3% ($P = 0.056$)	Patients in the CRT group were significantly older, had a poorer Eastern Co-operative Oncology Group performance status and had higher Charlson co-morbidity scores than those in the surgery group. This study has a small sample size in the CRT group
Moreno *et al.* (2017), J Thorac Oncol, USA [5] Cohort study (level 3)	A total of 300 patients aged ≥80 years with Stage I oesophageal cancer were included for analysis (definitive CRT group: 206 patients; surgery group: 94 patients) Treatment selection: not available CRT: concurrent CRT ± induction chemotherapy Surgery: partial or total oesophagectomy with or without a gastrectomy	Median follow-up time 5-Year OS rate OS (multivariate analysis)	13.9 months for all those patients CRT group: 20%; surgery group: 45% HR 1.3; 95% CI 0.92–1.82	This study had a relatively large sample size in both groups

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Kamel *et al.* (2018), Eur J Cardiothorac Surg, USA [6] Cohort study (level 3)	A total of 4600 patients with T1N0M0 oesophageal cancer were included for analysis (definitive CRT group: 2338 patients; surgery group: 2262 patients). PSM analysis was conducted to generate a total of 497 pairs of well-matched patients Treatment selection: not available CRT: radiotherapy Surgery: oesophagectomy	Median follow-up time 5-Year OS (unmatched patients) 5-Year cancer-specific survival (unmatched patients) OS (unmatched patients) 5-Year cancer-specific survival (matched patients)	Not available CRT group: 15%; surgery group: 67% ($P < 0.001$) CRT group: 24%; surgery group: 77% ($P < 0.001$) HR 3.67; 95% CI 3.03–4.44 CRT group: 38%; surgery group: 73% ($P < 0.001$)	This study had the largest sample size in both groups, and it also applied PSM analysis to balance patient selection bias

CI: confidence interval; CRT: chemoradiotherapy; HR: hazard ratio; OS: overall survival; PSM: propensity score-matched.

RESULTS

In 2011, Yamamoto *et al.* [2] conducted the first study comparing the survival of patients with clinical Stage I oesophageal cancer treated with definitive CRT with that of those treated with surgical resection. They included 54 patients treated with definitive CRT and 116 patients with surgery and found that 1-year and 3-year survival rates in both the definitive CRT group and the surgery group were comparable (CRT group: 98.1% and 88.7%, respectively; surgery group: 97.4% and 85.5%, respectively; $P = 0.78$). However, patients treated with definitive CRT had significantly lower 1-year and 3-year progression-free survival rates than those treated with surgery (CRT group: 84.6% and 70.1%, respectively; surgery group: 93.9% and 81.9%, respectively; $P = 0.04$). Their study indicated that definitive CRT seemed to be a viable alternative to surgery in patients with clinical Stage I oesophageal cancer. Reid *et al.* [3] also compared the effects of definitive CRT with those of surgery in treating clinical Stage I oesophageal cancer. They included only 10 patients treated with definitive CRT and 22 patients with surgery and also found that median and 2-year overall survival in both the definitive CRT group and the surgery group were comparable (CRT group: 68 months and 68.6%, respectively; surgery group: not available and 85.6%, respectively; $P = 0.236$). However, patients treated with definitive CRT tended to have a lower 2-year disease-free survival rate than those treated with surgery (CRT group: 68.6%; surgery group: 85.6%; $P = 0.069$). It should be noted that, in their study, patients were selected to receive CRT due to the fact that they were deemed unsuitable for surgery, on grounds of comorbidities and/or performance status, or their loco-regional diseases were considered too extensive for curative resection, or they personally chose CRT. Their small sample size could also influence the validity of their results. Therefore, their study indicated that definitive CRT seemed to be an alternative to surgery in patients with clinical Stage I oesophageal cancer who were unfit for surgery or declined surgical resection. Later in 2014, Park *et al.* [4] conducted another similar study comparing the effects of definitive CRT with those of surgery in treating patients with clinical T1N0M0 oesophageal cancer. They included 20 patients treated with definitive CRT and 264 patients with surgery. They found that the 3-year and 5-year time-to-recurrence rates in both groups were comparable (CRT group: 82.7% and 82.7%, respectively; surgery group: 84.5% and 80.7%, respectively; $P = 0.831$), whereas 3-year and 5-year overall survival rates in the definitive CRT group tended to be lower than those in the surgery group (CRT group: 76.8% and 58.5%, respectively; surgery group: 86.8% and 73.3%, respectively; $P = 0.056$). It should also be noted that most patients in the CRT group were medically unfit for surgery or declined the radical oesophagectomy. Moreover, the very limited sample size in the definitive CRT group could also influence the validity of their results. Therefore, similar to the previous study, they also indicated that definitive CRT could be an alternative to surgery for patients with clinical T1N0M0 oesophageal cancer who are unfit for radical surgical resection.

Recently in 2017, Moreno *et al.* [5] conducted a study on patients older than 80 years with Stage I oesophageal cancer, and they compared the effects of definitive CRT with those of surgery. They included 206 patients treated with definitive CRT and 94 patients with surgery and found that patients treated with definitive CRT had a lower 5-year survival rate than that treated with surgery (CRT group: 20%; surgery group: 45%). In the multivariate

analysis, CRT trended to result in worse overall survival compared to surgery [hazard ratio (HR) 1.3; 95% confidence interval (CI) 0.92–1.82]. Their study indicated that surgery may be superior to definitive CRT in treating elderly patients with Stage I oesophageal cancer. More recently, Kamel *et al.* [6] presented a similar study with the largest sample size comparing the effects of surgery with those of radiotherapy in treating patients with T1N0M0 oesophageal cancer from the Surveillance, Epidemiology and End Results database. They included a total of 4600 patients with early-stage oesophageal cancer (definitive radiotherapy group: 2338 patients; surgery group: 2262 patients). They found that the 5-year survival rate and cancer-specific survival rate in the definitive radiotherapy group were significantly lower than those in the surgery group (radiotherapy group: 15% and 24%, respectively; surgery group: 67% and 77%, respectively), and definitive radiotherapy was significantly correlated with poor survival compared to surgery (HR 3.67; 95% CI 3.03–4.44). Because of the unbalanced baseline characteristics between the 2 groups, they applied propensity score-matched analysis to generate 497 pairs of well-matched patients in the 2 groups. Still, they found that the 5-year cancer-specific survival rate in the definitive radiotherapy group was significantly lower than that in the surgery group (radiotherapy group: 38%; surgery group: 73%; $P < 0.001$). Their study indicated that surgery remained superior to radiotherapy in treating early-stage oesophageal cancer.

CLINICAL BOTTOM LINE

Definitive CRT resulted in worse overall survival and more recurrence in treating early-stage oesophageal cancer compared to surgery, although the evidence is scarce and of poor quality. Therefore, we would recommend that surgery still remains the standard treatment for patients with early-stage oesophageal cancer, whereas definitive CRT could be an alternative to surgery for patients unfit for surgery, although with slightly inferior outcomes.

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