

# Current standards and options in the treatment of squamous cell oesophageal carcinoma

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Traditionally, surgery is considered to be the best treatment for oesophageal cancer (OC) for locoregional control and long-term survival. Since the survival rates are around 25% at 5 years after surgery alone, a multidisciplinary approach that includes surgery, radiotherapy (RT) and chemotherapy (CT), alone or in combination, may be necessary. The place of each of these treatments, depending on the disease stage, is under intensive research to define optimal therapeutic strategies.

## **Surgery**

Surgical resection is a standard treatment option for localised OC, usually performed by right transthoracic or transhiatal approaches. Following recent studies [1–4], complete (R0) transthoracic *en bloc* oesophagectomy with two field lymphadenectomy (abdominal and thoracic) and gastropasty is considered, worldwide, as the approach of choice. Nevertheless, cervical lymphadenectomy seems to be useful in upper-thoracic and cervical OC [2,4].

The results in OC surgery vary a lot depending on the age of the series, their origin from expert centres or not and quality criteria regarding surgical technique and reporting. At 5 years, overall survival after surgery alone in expert centres was of around 34 to 50% [1, 2,5], with survival rates from 84% for stage I to 17% for stage III. Results of postoperative morbi-mortality and survival are significantly better in expert centres, leading to the recommendation of such surgery in high volume hospitals [6].

## **Combination of surgery, neoadjuvant and adjuvant treatments**

RT and CT could improve the control of local or general disease with the aim of (i) downstaging cancer, thus increasing resectability, (ii) eradicating micrometastatic disease, (iii) decreasing cancerous cell

dissemination during intervention and (iv) administering a complementary treatment without influencing postoperative mortality or morbidity.

## **Radiotherapy**

Significant increases in the resectability or survival were not shown in five randomised trials comparing neoadjuvant RT+ surgery versus surgery alone in OC. A recent meta-analysis found a non significant survival benefit of 4% at 5 years for preoperative RT [7]. Moreover, no overall survival advantage was observed for adjuvant.

## **Chemotherapy**

### *Neoadjuvant chemotherapy versus surgery alone*

Neoadjuvant CT was compared with surgery alone in OC in eleven randomised trials. In six trials survival benefits were observed in responders to CT, while a significant survival benefit was found in two studies. The most recent meta-analysis concluded that preoperative CT + surgery may offer a survival advantage over surgery alone for resectable OC, but with inconclusive evidence ( $P=0.15$ ) [8].

### *Adjuvant chemotherapy versus surgery alone*

Three phase III trials have compared adjuvant CT with surgery alone without demonstrating any overall survival benefit, except in the pN1 subgroup (52 versus 38%,  $P=0.041$ ) [9].

## **Neoadjuvant RCT**

Neoadjuvant RCT has been compared with surgery alone in patients with a resectable OC in nine randomised trials. Only two trials included enough patients to achieve correct statistical data [10,11] but none showed survival benefit for neoadjuvant RCT. The most recent meta-analysis concluded that

preoperative RCT allowed a survival benefit of 19% ( $P=0.002$ ) [16% for squamous cell carcinoma (SCC)] [12]. Persistently in these trials (i) the tumoural downstaging increases R0 resection rate, (ii) responder patients have better survival, (iii) 25% of patients after neoadjuvant RCT do not present any tumoural residue and (iv) no significant postoperative increase in morbi-mortality is observed.

### Exclusive treatments (without surgery)

Because of high rates of postoperative complications, many authors investigated whether oesophagectomy was necessary after neoadjuvant RCT.

#### *RCT alone versus radiotherapy alone*

Herskovic and colleagues [13] compared RT alone with RCT with 2-year survival of 10 *versus* 38% ( $P=0.005$ ), respectively. It is remarkable that (i) the grade 3–4 toxicity was higher in the RCT group, (ii) persistence or local recurrence was noticed in 40% of patients suggesting that additional surgery could have improved survival and (iii) 92% of patients presented small tumours (without lymph node involvement in 82%). A recent meta-analysis of 13 randomised trials comparing RCT to RT confirmed the superiority of RCT [14] with an absolute reduction of death by 7%, and a reduction in local persistence/recurrence rate by 12%. The downside is a 17% increase in grade 3–4 toxicity [14].

#### *RCT alone versus RCT followed by surgery*

Two randomised trials compared RCT alone with RCT + surgery for locally advanced SCC [15,16]. In the Stahl study [15], 3-year survival rates were not different (28% surgical arm *versus* 20% non surgical arm,  $P=0.22$ ). Survival was better in responders and local tumour control was worse in the non surgical arm. The 3-year survival rate was much higher in non responders undergoing R0 resection (32 *versus* 11%). In the Bedenne trial [16], responders to an induction RCT were randomised in a RCT + surgery group *versus* RCT alone, with no difference in 2-year survival (34 *versus* 40%,  $P=0.56$ ). Therapeutic mortality rates were 9.3 *versus* 0.8% ( $P=0.002$ ). Two-year survival without local progression was better in the surgery group (64.3 *versus* 40.7%,  $P=0.003$ ). These results question the role of surgery for locally advanced SCC treatment. Nevertheless, they do not mean that surgery has no further place but rather raise the question as to which patients will benefit most

from it. In fact, response to neoadjuvant treatment selects a patients group with good prognosis with or without surgery. For similar patients, a recent controlled study showed a 2-year survival rate of 52% for RCT + surgery [10]. This suggests that adding surgery to RCT for locally advanced SCC may result in improved local control and survival.

To conclude, the results of the latest randomised trials allow us to propose the following guidelines: surgery is the reference treatment to be used alone for stages I and IIa, or in a debatable association with CT or RCT as neoadjuvants for stage IIb. For locally advanced SCC (stage III) exclusive RCT should be considered only in morphological responder patients, allowing similar overall survival with less post-treatment morbi-mortality than RCT followed by surgery. However, adding surgery for those patients may result in improved local control and survival but should be performed in experienced centres where operative mortality and morbidity rates are lowest. Moreover, surgery should be kept in mind as salvage treatment in patients with no morphological response or persistent tumour after definitive RCT.

### Conflict of interest statement

None declared.

### References

- 1 Hulscher JB, Van Sandick JW, De Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;**347**:1662–9.
- 2 Altorki N, Skinner D. Should en bloc esophagectomy be the standard of care for esophageal carcinoma? *Ann Surg* 2001;**234**: 581–7.
- 3 Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg* 2008;**247**:365–71.
- 4 Nishihira T, Hirayama K, Mori S. A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. *Am J Surg* 1998;**175**: 47–51.
- 5 Mariette C, Taillier G, Van Seuning I, Triboulet JP. Factors affecting postoperative course and survival after en bloc resection for esophageal carcinoma. *Ann Thorac Surg* 2004;**78**:1177–83.
- 6 Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**:1128–37.
- 7 Arnott SJ, Duncan W, Kerr GR, et al. Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev* 2005; 4:CD001799.

- 8 Malthaner RA, Collin S, Fenlon D. Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database Syst Rev* 2006;**3**:CD001556.
- 9 Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;**21**:4592–6.
- 10 Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997;**337**:161–7.
- 11 Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005;**6**:659–68.
- 12 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.
- 13 Herskovic A, Martz K, al-Sarraf M, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;**326**:1593–8.
- 14 Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *Cochrane Database Syst Rev* 2006;**1**:CD002092.
- 15 Stahl M, Stuschke M, Lehmann, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005;**23**:2310–7.
- 16 Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol* 2007;**25**:1160–8.
- 17 Mariette C, Piessen G, Lamblin A, et al. Impact of preoperative radiochemotherapy on postoperative course and survival in patients with locally advanced squamous cell oesophageal carcinoma. *Br J Surg* 2006;**93**:1077–83.