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Neoadjuvant treatment in oesophageal cancer: the needs for future trials

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In view of the poor survival after surgery alone for oesophageal cancer, combination with chemotherapy seems rational. A concept of upfront chemotherapy is discussed and seems especially useful for these tumours. The published randomized trials, studying the effect of neoadjuvant chemotherapy do, however, not (yet) show an improved overall survival, apart from one study with a significant median survival benefit at an interim evaluation. The responding patients have in all trials a far better survival than the non-responders. The numbers of patients are small and results of other ongoing and future trials should be awaited. New trials testing high-dose chemotherapy with bone marrow support should be initiated.

Key words: **oesophageal cancer; neoadjuvant treatment; trials.**

The outlook for patients with oesophageal cancer is poor. Although peri-operative mortality has decreased substantially in the past decades, the 5-year survival rate is still about 10% or less in those patients with loco-regional disease who have been operated upon with curative intent.[1,2] Micrometastatic dissemination resulting in a high proportion of regional and distant failures are common events, especially in Western patients, who may present late, and frequently have T_{3-4},N+ tumours.[3–6] The situation in Asia, China and Japan is different, as this tumour type is among the most frequently observed malignancies, and where screening programmes have certainly resulted in a high proportion of stage I patients, with good results after loco-regional treatment alone. This aside, it appears justified to consider a patient with loco-regional cancer of the oesophagus as having advanced disease at the time of diagnosis. The use of systemic treatment in combination with local modalities (surgery and/or radiotherapy) seems rational.

Because of the relative rarity of this disease and the severe morbidity in many patients at the time of diagnosis, tumours of the oesophagus have not been systematically tested against a variety of cytostatic drugs. However, both squamous cell carcinoma and adenocarcinoma are chemotherapy-sensitive, with response rates of approximately 40–50% (somewhat less for adenocarcinomas) for various cisplatin-based combination regimens.[7]

What is the impact of timing of systemic therapy on the outcome? Should conventional post-operative adjuvant treatment be applied, as in node-positive breast cancer, or is there a rationale for pre-operative or *neoadjuvant* systemic treatment? Post-operative systemic chemotherapy after primary local treatment for oesophageal cancer has not been successful. After an oesophagectomy, whether by thoracotomy or by a transhiatal approach, many patients

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cannot be treated with systemic chemotherapy for a considerable time. It is impossible therefore to comply with the basic rule of adjuvant chemotherapy, that is to start systemic treatment as quick as possible.[8] No randomized trials have been reported.

The concept of neoadjuvant chemotherapy has been developed to induce early tumour regression, with improved local control when followed by subsequent surgery and/or radiotherapy, and an ability to identify responding and non-responding patients.[9,10] In addition, several animal studies have shown an increase in the labelling index of metastases after resection of the primary tumour, and a better survival when chemotherapy was given before resection.[11-14] Lastly, chemotherapy is likely to have a greater impact when given early in the course of the disease, when subclinical metastatic burden is low and the patient is best able to tolerate toxic side-effects.

Potential drawbacks of neoadjuvant chemotherapy include: the (theoretical) possibilities of delay in achieving local control; a risk of tumour spread from the primary site in case of a chemoresistant tumour; and the creation of an 'unnatural' tumour area with necrosis and fibrosis at the time of surgery in cases of chemosensitive cancers.

Several phase II trials have been published on pre-operative chemotherapy in oesophageal cancer, especially in locally advanced disease.[15]

Major responses with cisplatin-based combination chemotherapy have been documented in 15 to 70% with complete pathological responses in 4 to 10% of patients. Operative mortality seems to be comparable to surgery alone. The combination of cisplatin on day 1 and 5-fluorouracil on days 1–4 has been studied extensively, and has become a standard, against which new combinations are being compared.[16-19] Although pre-operative systemic treatment seems to be safe, and operability, resectability and post-operative mortality are comparable with surgery alone, no clear survival benefit has been demonstrated in the above-mentioned phase II trials, which, by their nature, are not appropriate for testing survival differences.

Until now, three prospective randomized trials have been published, comparing neoadjuvant chemotherapy followed by surgery vs surgery alone. Roth *et al.* treated 17 patients with epidermoid carcinoma after randomization with 2 cycles of cisplatin, vindesine and bleomycine before surgery, followed by a 6-month period of post-operative chemotherapy with cisplatin and vindesine.[20] Although patients responding to chemotherapy had a significantly prolonged survival (median: >20 months), overall survival was no different for surgery alone or neoadjuvant chemotherapy with surgery. Resectability and post-operative complication rate were similar. Schlag *et al.* reported in 1992 the results of a randomized phase III study, in which the duration of pre-operative treatment was dependent on a response evaluation after only 1 cycle with cisplatin and 5-fluorouracil; patients with no change or progression were operated upon at once, while responding patients were treated with another 2 cycles.[21] The response rate was 47%. Chemotherapy was associated with more post-operative complications, like sepsis and respiratory problems, and overall survival was not influenced by neoadjuvant treatment (median 10 months), but, as in the study by Roth, responding patients had a prolonged survival (median: 13 months) when compared with non-responders (median: 5 months).

A 4-arm study was reported in 1992 by Nygaard *et al.*, who randomized patients between surgery alone ($n=41$), pre-operative chemotherapy with cisplatin and bleomycin ($n=50$), pre-operative radiotherapy ($n=48$), or pre-operative chemoradiotherapy ($n=47$).[22] No data concerning response evaluation after chemotherapy or chemo-radiotherapy are available. Patients with pre-operative treatment had no survival benefit compared with surgery alone. Two prospective randomized trials were reported very recently in abstract form. Fok *et al.*[23] from Hong Kong presented results of a prospective randomized study on pre-operative chemotherapy (2 cycles of cisplatin and 5-fluorouracil) vs surgery alone. One hundred and sixty patients were randomized. There was a high resectability rate in both groups (88% vs 93%), and a high response rate after chemotherapy, with 19% complete responses and 32% partial responses. Median survival was the same for both groups: 12 months. The 5-year survival rate for responding patients was 52%, for non-responders 10%, and for the control group 11%. Kok *et al.*[24] presented results of an interim analysis of a similar study in which the duration of pre-operative chemotherapy was dependent on the response evaluation after 2 cycles of chemotherapy with cisplatin and etoposide; in case of a clear response, another 2 cycles were given pre-operatively, and in case of no response, the patient was operated on at once. In this ongoing trial, approximately 100 patients were randomized. With a median follow-up of 17.5 months there was a statistically significant median survival benefit after chemotherapy, not only for responding patients but also for the chemotherapy group as a whole. Final results with a longer follow-up are needed to draw definitive conclusions.

Two large scale phase III trials are now underway: the US Intergroup trial (Nr 0113) randomizing more than 400 patients with squamous cell carcinoma and adenocarcinoma to receive 3 neoadjuvant and 2 post-operative chemotherapy cycles with cisplatin and 5-fluorouracil vs surgery alone. This trial has recently stopped patient entry, and results are awaited. An ongoing European trial (the MRC trial from the UK) is investigating the effect of 2 cycles of chemotherapy with cisplatin and 5-fluorouracil followed by surgery vs surgery alone in patients with squamous- or adenocarcinoma. No definitive results from this trial will be available in the short-term.

Several phase II trials have discussed the value of neoadjuvant chemotherapy with concurrent radiotherapy, followed by resection. The rationale behind this may be the chance to eradicate a greater proportion of cells, including resistant subpopulations, from the start of treatment.[25] Also a smaller tumour mass may be more sensitive to radiation because of better central oxygenation.

A non-randomized phase II study by the SWOG and RTOG in the US, treating more than 150 patients pre-operatively with cisplatin and 5-fluorouracil plus 30 Gy of concurrent radiotherapy, resulted in a median survival of 12 months, which is no different from those found with surgery alone.[26] A randomized French study published in 1994, using 2 short cycles of cisplatin and 5-fluorouracil, interspersed

with 20 Gy of radiation followed by resection, showed no survival benefit in the experimental group of patients.[27]

Better results have been achieved with systemic chemotherapy and concurrent radiotherapy than with radiotherapy alone. Important data from such a randomized trial have been published by Herskovic *et al.* in 1992.[28] The trial was stopped after the accumulated results in 121 patients demonstrated a significant advantage for survival in patients who received chemotherapy and concurrent radiotherapy. No long-term survival data have been published yet.

What can we learn from the data available so far? Surgery alone seems to remain the standard of care for surgically treatable patients. The completion of the above-mentioned phase III randomized trials need to be available before a definitive place for neoadjuvant chemotherapy can be established. In several trials a survival benefit has been shown for those patients manifesting a major objective response to neoadjuvant chemotherapy. Although a response to chemotherapy may not be a totally independent prognostic factor, an intensification of the known chemotherapy schedules with bone marrow support by colony stimulating factors, and the implementation of new active compounds, with the aim of increasing the response rate (especially complete responses), should be issues for forthcoming research.[29,30] In the meantime the discovery of new tools to differentiate between responding and non-responding patients as early as possible in the period of pre-operative treatment, perhaps even before the start of treatment, should be pursued. If, eventually, neoadjuvant treatment should result in a better survival after surgery, then a randomized study, evaluating the best local treatment: surgery vs radiotherapy, should be initiated, including quality of life measurements.

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