Obstructive cancer of the oesophagus and gastroesophageal junction

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Introduction

Cancer of the oesophagus and gastroesophageal junction (GEJ) is diagnosed in about 400,000 patients per year. It is now the ninth most common malignancy worldwide and the sixth most common cause of cancer mortality.

Up to the early 1970s, more than 80% of oesophageal cancers were squamous cell carcinomas. However, epidemiological studies have shown a large increase of adenocarcinoma of the oesophagus and GEJ over the last 30 years in North America and Western Europe [1]. This alarming rise in the incidence of adenocarcinoma is thought to be linked to an increase in the incidence of Barrett metaplasia and subsequent degeneration.

Symptoms and signs

The vast majority of patients present with dysphagia and/or odynophagia as the main symptoms, irrespective of the type of tumour. Dysphagia is not a symptom unique to oesophageal malignancy. There are also non-malignant diseases that present with dysphagia as the cardinal symptom e.g. achalasia and reflux stricture. In benign disease, the onset of dysphagia is slow and weight loss is rather limited. In malignant disease dysphagia is progressive for solid food, eventually also occurring for liquids, although complete dysphagia, in Western countries at least, is rare. Nevertheless, up to 85–95% of patients with cancer of the oesophagus or GEJ first present with dysphagia and weight loss caused by obstruction of the oesophageal lumen by the tumour [2].

Typically, the symptom of dysphagia has been present for more than three months, as most patients seem to be unaware of its significance. Many patients have already adapted themselves to the progressive luminal obstruction by subconsciously changing their eating habits.

It is not uncommon that members of the patient' s family are the first to notice these changes in eating habits and bring these to the attention of their general practitioner. In a community survey Grannell et al. [3] found that only 17% of interviewed patients felt that cancer was a probable explanation for dysphagia, whereas for instance 80% would consider cancer a likely cause of a breast lump. This study highlights the evident need for an awareness programme of the potential significance of dysphagia as a symptom of obstructive cancer, if the prognosis for oesophageal cancer is to be improved. Dysphagia and its concomitant weight loss are generally considered to be signs of a more advanced stage, by which at least 50% of the oesophageal lumen is compromised and is causing obstruction to the free passage of the alimentary bolus. As a result, dysphagia is seen as a sign of a poor prognosis. However, dysphagia does not occur only in the advanced stage of disease. Indeed, in a minority of patients dysphagia is an early symptom as a reflection of a functional reaction, e.g. spasm of the oesophagus, to an early cancer. As a result, the correlation between obstructive symptoms and tumour stage is unreliable, especially in distinguishing between early (intramural) and advanced (trans- and extramural) tumour stage. Therefore, any patient presenting with obstructive symptoms requires a careful investigation not only to obtain a diagnosis but also to define the extent of the disease and subsequent therapy.

Technical evaluations

Assessing the extent of the disease is based on a number of technical examinations, besides medical history and clinical examination.

Spiral CT scan [4] and echoendoscopy (EUS) [5] including EUS guided fine needle aspiration (FNA) [6] are the key investigations in assessing the extent of the disease. However in patients with symptoms caused by a tumoural (organic) obstruction of the lumen the accuracy of staging may be impaired [7], particularly when attempting to perform an EUS, due

to the instrument not being able to pass the tumour. Dilatation of the tumoural part of the oesophagus-cardia preceding the EUS may be helpful but may also increase the risk of perforation and thus jeopardize the therapeutic options [8]. Modern spiral CT and PET, or nowadays PET-CT, may in part overcome the shortcomings of the ability to perform EUS. Moreover, PET scanning has the additional advantage of screening the whole body, increasing the detection rate of distant metastases [9,10].

Some data in the literature seem to indicate that tumours that cannot be passed by an echoendoscope carry a worse prognosis [5].

According to the findings from these examinations and the philosophy guiding the therapeutic strategies, additional investigation i.e. laparoscopy, thoracoscopy, NMR or bronchoscopy may be necessary.

Treatment

The therapeutic strategy is in the first place guided by the resultant clinical TNM staging. The strategy falls into two major groups – those patients presenting with a disease that still can be treated with curative intent and those patients presenting with incurable (stage IV) disease, for whom palliation is the only remaining option.

Patients fall into the category of palliation if they have distant organ metastases or distant lymph node metastases extending beyond the locoregional limits of the surgical field, or if presenting with extensive locoregional disease that precludes any curative treatment modality, e.g. malignant tracheoesophageal fistula, or in whom co-morbidity contraindicates any curative approach.

In all other patients treatment modalities aiming at cure may be considered. It is generally accepted that surgery is still the mainstay of any treatment modality with curative intent.

In the earlier stages of the disease, i.e. T1–2 (mostly non-obstructive tumours, with limited or no lymph node involvement), primary surgery is considered the treatment of choice. Its results exceed 90% 5-year survival for T1N0 tumours and over 60% for T2N0 tumours [11]. In more advanced stages of the disease (mostly obstructive tumours and thus in the majority of cases presenting with lymph node involvement on pathologic examination), 5-year survival after primary surgery is generally reported as 10–15% according to data from the literature [12]. However, these figures vary substantially according to the extent of the lymphadenectomy performed at time of surgery. Today there is an increasing body of evidence that 5-year survival after a more radical oesophagectomy and lymphadenectomy is much higher, varying between 25% and 35% for stage III disease after an R0 resection [11,13–16]. These figures are the gold standard to which al other therapeutic options aiming at cure should be compared. Some Japanese studies focusing on the value of three-field lymphadenectomy have even reported 5-year survival for stage III disease as high as 56% [17].

However, despite all efforts, a majority of patients will still die from general and/or locoregional metastases. This has resulted in an interest in combined therapeutic modalities. Many therapeutic schemes using chemotherapy and radiotherapy as monotherapy, preceding or following surgery have been tried in order to improve survival.

Most chemotherapy regimens use a combinations of cisplatin and 5-fluorouracil (5-FU). Some have used vindisine, bleomycine, mitomycine and more recently taxanes. Radiotherapy varies widely between 20 and 60 Gy with various designs of dosage fractions and radiation fields.

Although a number of phase II trials did show encouraging results with response rates of 50% or more, most prospective controlled randomised trials were either deceiving in terms of long term survival or showed conflicting results [18]. Bhansali in 1996 [19] published a meta-analysis of 12 published randomised controlled trials to assess the efficacy of neoadjuvant or adjuvant chemotherapy on survival in oesophageal cancer. He could not observe any significant survival benefit from the combined treatment arm. A Cochrane review published in 2001 by Malthaner et al. [20] found a small however significant survival benefit but only at 5 years and only for intrathoracic tumours.Finally, two major randomised controlled trials comparing neoadjuvant chemotherapy and surgery versus surgery alone have been published recently showing conflicting results. The US trial published by Kelsen in 1998 [21] showed no improvement in outcome by adding a combination of neoadjuvant cisplatin and 5-FU (overall 2-year survival of 35% and 37% respectively). The British MRC trial however indicated a significant overall survival benefit at 2 years in the combined arm of 43% versus 34% for the surgery alone arm [22].

The value of preoperative radiotherapy alone has been studied by a Cochrane meta-analysis of five prospective randomised trials. With a median follow-up of 9 years in 1147 patients, this analysis indicated an overall reduction in risk of death of 11% and a non-significant survival benefit of 4% at 5 years,

concluding that there was no clear evidence of an improvement in survival for patients with potentially resectable oesophageal cancer [23].

Combining the theoretical advantages of local irradiation and the radiosensitizing properties of chemotherapy together with its potential systemic effect on micrometastases, much has been expected of neoadjuvant chemoradiotherapy. At least nine prospective randomised trials have been published. Except for one trial, no significant overall survival advantage favouring the combined arm could be noted [18]. The trial that did show a significant difference was criticised because of the poor result of the surgical arm, most likely due to an unselected group with a too advanced disease [24]. Moreover, overall survival rates in the different trials and in both arms were 10–30%; rather low, considering that most trials also included early stage cancers. Nevertheless, a meta-analysis [25] of these trials suggested a survival benefit at three years in favour of the combined arm.

From a number of mostly non-randomised trials it appears that the subset of patients showing a complete response are the ones that seem to benefit most from the induction chemoradiotherapy with 5-year survival figures of 30–71% [18].

Unfortunately at present, there are no specific tests or markers to indicate which patients will be good responders and which ones will not. In addition, restaging after induction therapy is well known to be inaccurate. It might well be that the non-responders are paying the price by losing precious time before coming to surgery, and this might be the most likely reason why the overall results do not show a survival benefit compared with primary surgery [26].

More recently, PET scanning has been used as a tool to assess the response to chemotherapy at an early stage i.e. after the first cycle of chemotherapy. This has resulted in trials selecting those patients that show a response on PET-scan after the first cycle of chemotherapy to continue with the full induction therapy before surgery. In contrast, the non-responders can be treated either immediately by surgery or by some form of palliative treatment [27,28].

In parallel, the use of PET as a tool to assess the early response has also generated interest in the use of chemoradiation as a definitive treatment without surgery. A number of randomised trials are evaluating the results of definitive chemoradiation versus chemoradiation followed by surgery.

The initial results from these trials indicate a similar outcome between the two arms on the basis of 3-year survival. However, one criticism of these trials is the rather high surgical mortality as well as the low survival figures (overall 3-year survival of 28% after surgery as compared to the gold standard of primary surgery). Also rather worrying is the high percentage of locoregional recurrences of up to 60% in the non-surgical arm as a result of incomplete sterilisation of the primary tumour and/or locoregional lymph nodes [29].

Therefore, attention has turned to the assessment of the value of adjuvant therapy. This interest has been stimulated by a trial on the use of adjuvant chemoradiotherapy after surgery for gastric cancer [30]. From this trial, it appeared that patients with positive lymph nodes benefit from such therapy. As this study also included a subset of patients with adenocarcinoma of the cardia it may well be that such adjuvant regimens will also prove to be beneficial when applied to adenocarcinomas of both the GEJ and distal oesophagus [31].

On a more experimental level, research is focusing on targeted therapy on a molecular basis but thus far, no conclusive data are available [32].

Palliative treatment

For patients who have an incurable cancer or who are medically unfit for treatment with curative intent, palliation of symptoms with, if possible, a prolonged survival, is the aim of therapy.

Physicians who are responsible for the care of such patients must accept the obligation to ensure that palliation occurs early and effectively, to guarantee the best quality of life for the remaining limited lifespan. In such a setting, cost benefit consideration may play an important role. Relief of dysphagia, odynodysphagia, and malnutrition, and if possible prolonged survival with a good quality of life are the essentials of any programme of palliation. Depending on the physical condition as well as the available expertise a wide range of therapeutic modalities can be utilised.

Palliation of an obstructive tumour causing dysphagia, odynophagia and malnutrition can be achieved in different ways.

Peroral dilatation can be used mostly as an initial therapy to restore patency prior to a more definitive treatment. The most common form of dilatation is performed using the Savary bougies. The dysphagia relief typically last only a few days or weeks [33].

The use of Nd:Yag laser ablation of obstructing oesophageal cancer is well established. However, laser therapy is expensive, is more difficult to use and carries a higher risk [34–36].

Absolute alcohol or other sclerosant solutions injected into exophytic tumour masses can safely provide relief from obstruction at much less expense than laser therapy [37]. Good results in relieving dysphagia have been described by using photodynamic therapy (PDT) [38].

Plastic or metal expandable stents offer a number of distinct advantages over other forms of palliation, in particular relief of dysphagia on a more permanent basis. Self-expanding stents offer a better possibility of adequate lumen restoration with less incidence of migration. These stents are also particularly useful to seal off [39,40] malignant tracheoesophageal fistulae.

Finally, external radiotherapy, and even better, brachytherapy are also effective means to palliate dysphagia. A recent randomised controlled trial comparing stenting versus brachytherapy has indicated a more prolonged relief of palliation by brachytherapy with fewer complications resulting in a superior quality of life. This study recommends the use of brachytherapy when a more prolonged palliation is required. Stenting should be the treatment of choice when a short-term survival (e.g. 4 to 6 weeks) is expected and in case of resistance to brachytherapy [37,41,42].

None of this array of techniques is ideal and optimum therapy often requires at least two sessions of such procedures to provide adequate relief of dysphagia, and therefore requires sufficient familiarity with these techniques as well as expertise from the treatment team.

These novel techniques and refinements of existing technologies have resulted in a sharp decrease in the need for surgical palliation. In particular, the bypass procedure has few indications given the often limited life expectancy of patients with such treatments [43].

As many of these patients will present with a poor nutritional status, nutritional support is often mandatory. Enteral feeding can be administered through a percutaneous endoscopic gastrostomy if the scope can pass the tumour. If not home total parenteral nutrition (TPN) through a subcutaneous device may offer sufficient supplementation of nutrition if only a short-term need is foreseen. Surgically placed gastrostomy should be avoided unless no alternative is available.

A substantial number of patients treated with curative intent will die eventually from recurrent disease, mostly systemic. However, a small number will develop localised obstructive recurrence. If their general condition permits, combined chemoradiotherapy possibly with an endoluminal procedure may offer long-lasting relief of dysphagia. In the remaining patients presenting with more generalised disease again a choice has to be made amongst one of the available endoluminal procedures.

Whatever type of palliative method, close follow-up is mandatory as problems like stent migration or recurrence of tumour growth do occur, requiring adjustment or change of the therapeutic modality.

Given the great variety of therapeutic tools it is difficult to provide high-level evidence-based guidelines and therefore mostly, the treatment plan is left to the physician' s personal preference. No one palliative method is ideal and optimum therapy has to be tailored according to each individual case, especially for those patients who have poor performance status.

Conclusions

Obstructive carcinoma of the oesophagus and GEJ reflects an advanced stage of the disease in the vast majority of the patients.

Given the tendency of early lymphatic spread both in oral and aboral direction a meticulous clinical staging is mandatory. Endoscopy, EUS +/– FNA, spiral CT and PET-scan are the most important tools in this respect.

Therapeutic strategies aiming at cure include primary surgery for resectable cancer (cT1-T3) and limited peritumoural lymph node involvement. In more advanced but still locoregional disease (cT4, more extensive and/or more distant lymph node involvement) a combined treatment modality in particular induction chemoradiotherapy is the treatment of choice. Complete responders seem to be the subset of patients who benefit most but unfortunately, no markers are available to predict response. More recently, it has been suggested that adjuvant chemoradiotherapy may beneficial in particular in patients with positive nodes but this needs to be further investigated within the framework of randomised controlled trials.

For patients with incurable modalities aiming at cure, palliation of symptoms is the aim of therapy. Stenting or brachytherapy seems to offer the best guarantee for a durable relief of dysphagia.

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