Outcome of Palliative Care Regimens in Patients with Advanced Oesophageal Cancer Detected During Explorative Surgery

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Abstract. Background: The outcome of different palliative regimens was investigated in patients with incurable oesophageal carcinoma identified during surgical exploration. Patients and Methods: Between January 1992 and December 2002, 203 patients with oesophageal cancer underwent surgery after a standard staging procedure including computer tomography and endoscopic ultrasonography. The data from 78 patients, rendered incurable at exploration and who subsequently underwent palliative interventions, were analysed retrospectively. Results: The median survival in the whole group was 8.9 (1-105) months. Patients treated with chemotherapy had a higher median survival of 11.6 months compared with that of the other palliatively-treated patients: 8.4 months (p=0.003). Overall, intraluminal stenting was the palliative measure of dysphagia in 25 patients (32.3%). Conclusion: Patients with incurable oesophageal carcinoma have a poor overall survival of less than 9 months. Stenting is frequently (32%) needed for ultimate palliation of dysphagia after primary treatment. In a selective group, palliative chemotherapy offered a survival benefit compared with other treatment modalities.

The incidence and mortality of oesophageal carcinoma has increased during the last decade, especially in adenocarcinoma located predominantly in the lower third of the oesophagus (1-21). The reported overall incidence of oesophageal cancer is currently 3.2 per 100,000 and is the sixth most frequent cancer type world-wide (16).

Surgery is the only curative option, providing local tumour control with survival rates superior to those afforded by non-surgical treatment (22). Even after successful surgery, the prognosis is relatively poor with a median survival of 2 years and a long-term survival of only 20%. Moreover, oesophagectomy has a substantial morbidity and mortality with a negative impact on the quality of life for several months (9). Therefore, palliative resection is not always acceptable and proper pre-operative staging is necessary to select those patients who will benefit from curative resection. Currently, multidetector computed tomography (CT), endoscopic ultrasonography (EUS) in combination with fine-needle aspiration (FNA) and ultrasound of the cervical region are routinely used in staging patients with oesophageal cancer (25). In recent decades, positron emission tomography (PET) with 18-F-fluorodeoxyglucose (FDG) has gained acceptance as a non-invasive staging modality, but its exact role in pre-operative staging is still questionable (5, 13).

Despite improvements pre-operative staging, non-invasive methods are not yet completely reliable in determining resectability and in detecting distant metastases (14). Therefore, a considerable rate of locally advanced disease (T4) and/or distant metastases (M1) is encountered during the explorative phase of an intended curative resection. Depending on the pre-operative work-up, the reported rates of explorative surgery only ranged from 10% to 60% in these patients (19, 24).

The main concern in patients with irresectable disease and limited life expectancy is to offer palliative treatment with relief of dysphagia. Palliative treatment mainly consists of non-surgical techniques, including intraluminal stenting and/or radiotherapy (2, 12). Chemotherapy may also lead to tumour regression and palliation of symptoms, but in most cases only for a limited period of time. (18) In locally advanced stages, neo-adjuvant chemotherapy, or even chemo-radiation followed by oesophagectomy, may become a reasonable approach (14, 17). Data regarding palliative treatment and survival are scarce in patients with incurable stages of oesophageal carcinoma who had undergone unnecessary explorative surgery. In order to justify the
possible side-effects of palliative chemotherapy, a careful selection of patients with reasonable prognosis is required. Accurate determination of the prognosis focused on those patients with irresectable disease at explorative surgery would, therefore, be desirable.

The aim of this study was to investigate the outcome of different palliative regimens in terms of survival, relief of dysphagia and formation of distant metastases, in patients after surgical exploration only, and to examine the surgically-related morbidity and mortality.

Patients and Methods

Between January 1992 and December 2002, 203 patients with histologically-proven malignancy of the oesophagus or gastro-oesophageal junction were found to be eligible for potentially curative resection. Of these patients, 125 (62%) were curatively resected, while 78 patients (38%) underwent exploration only because of locally advanced disease and/or distant metastases established during surgery. Exploratory laparotomy was performed in 65 patients (83%) and a laparothoracotomy in 13 patients (17%).

This retrospective study focused on the 78 patients with an irresectable and/or incurable oesophageal carcinoma. All the characteristics are summarised in Table I. All the medical records were reviewed in order to investigate the post-operative details, type of palliative treatment, localisation of metastases and follow-up data, based on clinical examination.

Based upon further treatment, four subgroups were recognised: best supportive care (I), oesophageal intraluminal stenting (II), palliative radiotherapy (III) and chemotherapy (IV).

All the data collected from the medical records were stored in a database. Survival rates were calculated by the Kaplan-Meier method for the entire cohort, as well as for subgroups, based on the type of palliative treatment. To assess the types of palliation, the time between initial radiotherapy and chemotherapy and eventual stent placement was of interest in groups III and IV, while the time between exploration and stent placement was examined in group II.

The log rank test was used for comparison of survival curves. The Chi-square test was used to compare the period of palliation in the different groups regarding stent placement. A $p$ value $<0.05$ was considered significant.

Results

Complications of surgical exploration. The morbidity of surgical exploration was relatively low. Three patients (3.8%) presented minor post-operative complications (Table I). However, one patient died (1.3%) of unknown cause 5 days after the surgical procedure.

Palliative measures. The most frequently implemented palliative measure was relief of dysphagia. According to the type of palliative treatment, the remaining 77 patients were divided into four groups (Figure 1). Group I (n=7; 9%) consisted of patients with the best supportive care, as they did not wish any other form of palliative treatment. Group II (n=16; 21%) was palliated by stenting. Group III (n=28; 36%) received palliative radiotherapy on the primary tumour. The group IV patients (n=26; 34%) were treated in a phase II chemotherapeutic study with carboplatin, 4-epiadriamycin and teniposide (15). Based on adequate tumour response, 17 out of these 26 patients (65%) underwent a second exploration, followed by oesophagectomy in ten patients (13%). Seven patients still had an irresectable tumour during the second laparotomy and two of them received intraluminal stent, resolving dysphagia. Three out of the ten patients who had a curatively-intended resection after chemotherapy developed a locoregional recurrence and two were palliated afterwards by intraluminal stenting. In the radiotherapy group (group III), six patients (6/28; 21%) developed severe dysphagia and subsequently received an intraluminal stent after a median period of 21 (range 8-41) weeks.

Palliative treatment for severe dysphagia consisted of local treatment using intraluminal stenting and/or radiotherapy (n=44; 57%). Chemotherapy (group IV: n=26; 34%) was mainly used to achieve longstanding palliation or to reduce the tumour size in order to make a further attempt at surgery. In four out of these 26 patients (15%), dysphagia was relieved by insertion of a stent after chemotherapy. Of the 28 patients who received radiotherapy (group III), six

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GEJ: gastro-oesophageal junction.
patients (21%) developed severe dysphagia and received a stent (Figure 1). No patients in group II underwent secondary stenting. Overall, intraluminal stenting eventually solved the dysphagia symptoms in 25 patients (32.3%). After a previous primary palliative treatment, stenting was still necessary in ten out of the 54 patients (19%; groups III and IV). The time from initial treatment to stenting was equal (p=0.052) in these groups.

Clinical expression of tumour outgrowth. Nineteen new metastases were diagnosed in 14 patients (18%) after a median follow-up of 42 (range 4-135) weeks. In group I, brain metastasis occurred in one patient. The intraluminal stenting group II showed nine metastases (peritoneum n=2, lung n=2, supraclavicular n=2, brain n=1, liver n=1, skin n=1) in five patients. In group III treated with radiotherapy, seven metastases (bone n=2, peritoneum n=2, liver n=1, brain n=1, supraclavicular n=1) were diagnosed in five patients. In group IV patients who received chemotherapy, two patients developed one metastasis (bone n=1, supraclavicular n=1) after oesophagectomy. Three other patients (30%) in this group developed a local recurrence after oesophagectomy. There were no significant differences between the number and time of development of metastases in the different groups.

Median survival. The median survival of all patients after initial explorative surgery was 8.9 (1-105) months excluding post-operative deaths (Figure 2). The calculated 1-year, 2-year and 5-year survivals were 34.6%, 12.8% and 1.3%, respectively. Survival was not different between groups I, II and III, with median survivals of 8.6 (1.6-14.5), 5.1 (2.2-23.3) and 8.4 (1.5-40.4) months, respectively. However, survival was significantly higher for those treated with chemotherapy 11.6 (3.3-105.5) months (p=0.006x; Figure 3).

Discussion

In this study, explorative surgery in patients with oesophageal cancer was accompanied by a morbidity of 3.8% and a mortality rate of 1%. Irresectable disease at the time of explorative surgery had a devastating prognosis with a median overall survival of 8.5 months and severe dysphagia in about half of these patients. During follow-up, 18% of the patients developed new metastases. Chemotherapy, whether followed by resection or not, led to better survival compared with other treatment forms.
A variety of palliative regimens exists to alleviate dysphagia in the advanced stages of oesophageal cancer. The choice of method varies according to the anatomical features of the malignant obstruction, patient preferences and available expertise. Recent studies showed that palliation with single-dose radiotherapy seems to be more effective than intraluminal stenting in terms of dysphagia (6, 7). In our study, we found that, due to the need of stent placement in ten out of 54 patients in groups III (21%) and IV (15%) after initial palliative treatment, stenting often seemed to be the last resort palliative method to solve dysphagia, as described by Kaneko et al. (11).

Chemotherapy or chemoradiotherapy is directed against the entire tumour bulk and may, therefore, be helpful in relieving dysphagia. For patients with incurable disease, cisplatin-based chemotherapy appeared to be as effective as radiotherapy for the palliation of dysphagia (10, 17). However, the response rates were relatively low (up to 40-60%), leaving a substantial group of patients with no symptomatic improvement. The major drawbacks of systemic therapy are the general toxicity and undesired gastrointestinal side-effects. On the other hand, chemotherapy also had an impact on distant metastases with symptom relief and quality of life improvement in these patients, which plays a greater role in determining the clinical benefit (10). These patients should be selected carefully, based on their general health condition.

External radiotherapy has been used extensively for squamous cell carcinoma of the oesophagus, but only with symptomatic palliative intent. External radiotherapy, usually combined with intraluminal irradiation, is safe and effective to ensure normal swallowing function and seemed to contribute to prolonged survival (8, 26). Moreover, the quality of life after single-dose brachytherapy was more favourable to that of stent placement alone (7).

The use of expandable metal stents has gained acceptance as a cost-effective and safe alternative in the palliation of malignant oesophageal obstruction (12, 20). The introduction of the endoprothesis through the tumour results in an immediate relief of dysphagia. Tumour overgrowth is a disadvantage in this type of palliation and is strongly related to survival, which is usually short in these patients. Thermal palliative treatment, including laser ablation or photodynamic therapy, offers similar degrees of relief from dysphagia and at lower cost, as shown in two randomised trials (4, 15).

From our data, radiotherapy was not able to palliate dysphagia in all the radiated patients during follow-up. As a result, six out of the 28 radiated patients (21.4%) needed an expendable stent. For the group of patients who were treated with chemotherapy, four of the 26 patients had recurrent dysphagia, which was relieved by intraluminal stenting. However, physicians should make a tailored choice of palliation method, considering the risks and benefits. Because of the lack of large prospective trials, it is premature to claim the superiority of one treatment over others.

Tumours growing into adjacent organs (T4) and stage IV tumours, which are not candidates for resection, have a very poor prognosis. In this study, the median survival was 8.9 months with a 5-year survival of 1.3%, which is comparable with the data from the literature (3, 15, 23). Some patients were involved in a phase II trial followed by curative resection at a second surgical attempt, leading to overestimated survival in this group of patients.

The strength of this retrospective analysis lies in the uniform and ultimate staging of all the patients by surgery, making them a homogenous group. Patients with resectable or incurable stage oesophageal carcinoma were shown to have a very short life expectancy and a substantial number of patients developed metastases. Management leading to an improved quality of life is more pronounced than clinical treatment of the disease. Therefore, the search for better pre-operative staging is warranted to prevent unnecessary explorative surgery in such a group of patients.

References


