Pancreatic and hepatobiliary cancers: adjuvant therapy and management of inoperable disease

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Introduction

The overall survival rate of patients with pancreatic and hepatobiliary cancers is extremely disappointing. At diagnosis, nearly 90% of the patients in an unselected population are inoperable, either because of local unresectability as a result of overgrowth to adjacent, non-resectable organs or because of the presence of distant metastases. Moreover, many of the patients are too far along in life for active treatment. Of the remaining 10% that are eligible for curative resection, most, or about 90% of the candidates, will have cancer that recurs, often locally but also at distant sites. The present interest in the development of new treatment approaches in these cancers should be looked upon in the context of a surgical failure rate generally exceeding 99%. The poor results are seen in registry-based mortality data and in overviews of published literature [1-4]. This presentation will focus on the non-surgical treatment of patients with a primary tumour without evidence of distant metastasis. An accompanying presentation by Dr van Cutsem will describe treatments of patients with known metastatic disease.

Has any progress been made?

The intensity in staging will not improve the overall treatment results, but may influence the results in subgroups. Thus, greater possibilities to detect unresectability at diagnosis before surgery will not only improve the results in laparotomised patients but in non-laparotomised patients as well. Whether apparently more favourable results seen in some reports (see below) during the past decade are a result of this stage migration (Will Rogers phenomenon) or an effect of more efficient treatments is not known. A marked lack of properly controlled trials is evident and the few randomised trials that have been made are small and thus underpowered. Few treatments for pancreatic and hepatobiliary cancers can be considered 'evidence-based'. The presentation below of the most recent attempts to improve treatment outcome in patients without known distant metastatic disease should be looked upon from the perspective of this absence of precise knowledge about whether any progress has actually been made.

Palliation is paramount

The palliation of patients with pancreatic or hepatobiliary cancer is mainly focused on the relief of the most common symptoms (i.e. obstructive jaundice, gastric outlet obstruction and pain). Palliative treatment, however, also must focus on the emotional symptoms created by the knowledge of a grave cancer diagnosis with a short expected survival and the concomitant social and existential problems. The term 'best supportive care' emphasises the multidisciplinary attention to the individual's overall human needs in all phases of the disease.

The possibilities to relieve obstructive jaundice, being present in about 80% of the patients, were improved some 10 to 15 years ago after the introduction of stenting procedures that are more efficient. Several randomised studies have shown that an endoscopically or percutaneously placed endoprosthesis relieved the obstruction as efficiently as a surgical bypass procedure [5-8]. Although a non-operative procedure resulted in recurrent jaundice and cholangitis more frequently than with a surgical procedure, the continuous development and improvement in the care of the stented patients make the non-invasive procedure the preferred treatment whenever technically possible. It has also reduced costs considerably [9]. On the other hand, improved surgical techniques have diminished the mortality and morbidity rates after bypass surgery [10].

Symptoms of nausea and vomiting occur frequently in patients with pancreatic and biliary can-
Adjuvant therapy: randomised trials

The proportion of pancreatic cancer patients who have considerable pain is high. Besides pharmacological pain management with appropriate analgesic medications, various celiac nerve blocks may result in substantial pain relief. Nerve blocking can be done percutaneously or during laparotomy; more recently, laparoscopic transthoracic splanchnicectomy has been used for pancreatic cancer pain management [14,15]. At present, no results are available to justify palliative resection as a debulking procedure to relieve pain or other symptoms [16].

Attempts to improve tumour control

In addition to surgery, ultimately failing in 99% of the patients, chemotherapy and radiotherapy or combinations of the two modalities have been extensively undertaken, both before and after surgery, as well as in patients in which surgery is not considered at all. Although the distinctions between adjuvant therapy after apparently curative surgery and neo-adjuvant therapy before surgery for a potentially operable tumour to decrease recurrence rates, pre-operative therapy for an inoperable tumour to cause down-staging and facilitate resection and definite non-surgical therapy in locally inoperable disease are theoretically clear, this has not always been the case in some trials. Therefore, all non-surgical treatments for primary, non-metastatic disease are reviewed.

Adjuvant therapy: randomised trials

Five randomised studies of adjuvant (radio)chemotherapy following pancreatic resection for cancer are available. A modified FAM regimen (5-fluorouracil (5-FU), doxorubicin and mitomycin-C) was given every 3 weeks for six cycles after resection [17]. Of 110 patients with radical pancreatic resection, 61 were eligible for randomisation. The median survival in the treatment group was 23 months as compared with 11 months in the control group (p = 0.02). The difference was attributed to a survival benefit in the treatment group during the first 2 years; no difference was observed between groups in survival after the first 2 years. The toxicity from FAM was significant, with only 13 of 30 (or 43%) patients completing all six cycles.

A large Japanese randomised study of 158 patients with pancreatic cancer could not detect any benefit from postoperative chemotherapy using 5-FU and mitomycin C [18]. The study, only reported as an abstract, showed, however, a significant survival benefit for gallbladder cancer (n = 112) but no such benefit was observed for bile duct (n = 118) and periampullar or pancreatic cancer (n = 48).

5-FU together with external radiotherapy following resection has been used in three randomised trials versus a surgery alone group [19–21]. In the first trial, performed by the Gastrointestinal Tumour Study Group (GITSG), 5-FU was administered together with 40 Gy of external radiotherapy to 22 patients after radical pancreatectomy [19]. A statistically significant difference in survival was found between the treated patients and 21 non-treated controls (43 vs. 18% survival after 2 years and 18 vs. 8% after 5 years, p = 0.05). Similar results were reported from a phase II study using the same regimen of postoperative radiation and 5-FU treatment [22]. In these studies, good tolerance to the treatment regimen was noted.

In the second trial, performed by the European Organisation for Research and Treatment of Cancer (EORTC) [20], split-course chemoradiation as used in the GITSG trial was administered without maintenance chemotherapy. Totally, 218 patients were randomised, 119 with pancreatic head cancers and 109 with periampullary cancers. In patients with pancreatic cancer, median and 2-year survival rates were 17 months and 37%, respectively, for patients (n = 58) randomised to chemoradiation and 12 months and 23%, respectively, for patients randomised to the control arm (n = 61; p = 0.1). As in pancreatic cancers, there were no significant differences among patients with periampullary cancers. Overall, therapy was well tolerated but 22% of the patients in the chemoradiation arm in fact did not receive any treatment because of postoperative morbidity or patient refusal after randomisation.

The ESPAC-1 trial, performed in Europe, randomised almost 600 patients with resected pancreatic and periampullary cancer and preliminary results were presented at the American Society of Clinical
Oncology meeting in May 2000 [21]. The patients were randomised to surgery alone, or surgery plus chemoradiation as given in the GITSG-trial, chemotherapy using 5-FU and leucovorin, or surgery plus chemoradiation. Of the first 541 randomised patients, 285 were included in a 2 × 2 factorial design, 188 in a non-factorial comparison of chemotherapy alone and no adjuvant therapy and 68 in a similarly non-factorial comparison of radiochemotherapy alone with no postoperative therapy. The interim analysis showed that patients randomised to chemoradiation had a slightly worse survival after the first year than those not randomised to chemoradiation, and therefore on the recommendation of the data monitoring committee recruitment of patients to the radiotherapy question was terminated. The trial continues to randomise patients between surgery alone and postoperative chemotherapy since the interim analysis has indicated a survival gain for the chemotherapy group. The results are, however, not yet conclusive since the results differ between randomisation strata [21].

Evidence that adjuvant treatment should routinely be used in pancreatic cancer is presently not available. The small US GITSG study [19] has been discussed extensively during the past 15 years and the interpretation of the apparently positive trial data has varied considerably. The methodological weaknesses of the trial are so pronounced that it cannot form the basis for a recommendation of general treatment outside clinical trials. This is further supported by the EORTC trial [20]. The trial is negative (p = 0.1) but underpowered (n = 119). A joint committee of US co-operative groups recently reached a conclusion to the contrary [23]. Even if the committee recognised that "purists will demand to know where the no-treatment arm is to be found", it suggested a study (RTOG 9704) that has two active post-surgical chemoradiation arms [23]. The trial data, together with the positive results of the Norwegian trial [17], indicate, however, that further, properly controlled trials are important. In Europe, the ESPAC-1 will roll into ESPAC-3 randomising between surgery alone, 5-FU with leucovorin and gemcitabine. The future of adjuvant treatment of pancreatic and periampullar cancers is dependent on the results of this and comparable trials. In hepatobiliary cancer, there is likewise no evidence that chemotherapy or radiochemotherapy should be part of the postoperative routine.

**Adjuvant and neo-adjuvant therapy: non-randomised trials**

Different centres have reported median survivals ranging from 20–25 months after tumour resection in selected groups of pancreatic cancer patients that have been given multimodal neo-adjuvant or adjuvant treatment [24–32]. Long-term survival has usually been between 10 and 20%. Whether the apparently favourable survival reported from the above-mentioned treatment series is an effect of patient selection or the results of the (neo-)adjuvant treatment is unclear. In one of the reports, it was reported that only 12% of eligible patients received the intensive adjuvant therapy [29]. A noteworthy finding is that in some of the reported series of selected patients median survival of about 20 months after tumour resection has also been seen for patients receiving surgery alone [24]. This uncontrolled evidence, although rather extensive in terms of number of publications, does not change the conclusions reached from the randomised trials.

The situation described above for pancreatic cancers is analogous in hepatobiliary cancers. Consequently, curative surgery can seldom be performed, and if performed, the surgical resection margins are often compromised [3]. Pre- and postoperative or definitive chemoradiation has therefore been tried as it has in pancreatic cancer. The lack of knowledge of the effects of the non-surgical treatments is, however, even more pronounced since there is only one randomised trial [18] (see above) and the phase II trials are mostly small.

**Definite chemoradiotherapy in inoperable disease**

Two randomised trials have provided some evidence that chemoradiation is slightly superior to either modality alone in patients with inoperable pancreatic cancer. In a trial performed by the GITSG that included 194 patients, a slight gain in survival was seen when 5-FU was added to postoperative radiotherapy (40 Gy or 60 Gy) compared with radiotherapy alone (60 Gy, median survival 8 months vs. 5 months, p < 0.01) [33]. Chemotherapy alone (the SMF regimen) was inferior to the combination of 5-FU and radiation (54 Gy, median survival 8 months vs. 10.5 months, p < 0.02) in a trial including 43 patients [34]. In another randomised trial again performed by the GITSG, doxorubicin and radiation were compared in 157 patients with 5-FU and radiation. In this study, however, there was no evidence of superiority for either schedule [35]. Several attempts have been tried to intensify treatment even further using various schedules of combinations of chemotherapy and radiotherapy without any evidence of survival prolongation [36,37] or possibly some evidence of survival prolongation [38]. Similar survival results, however, have also been reported in older, rather
large series of histologically verified unresectable pancreatic carcinomas [39].

External radiotherapy, with or without concurrent chemotherapy, can palliate symptoms and occasionally result in long-term survival for patients with unresectable or recurrent biliary cancers [40]. Since these cancers are surrounded by several dose-limiting structures, the radiation technique must be optimised to reach the necessary radiation doses to have any significant impact on tumour control rates [41]. Even so, local tumour control is uncommon. Whereas several investigations have reported survival prolongation of postoperative radiotherapy in perihilar cholangiocarcinomas [28,42-45], Pitt and co-workers [46] found no such evidence of survival prolongation.

**Intraoperative radiotherapy, other local irradiation modalities and tumour destructive methods**

The insufficient results achieved with external beam radiation for pancreatic and hepatobiliary cancers, whether combined with chemotherapy or not, have prompted the exploration of various brachytherapy modalities, usually utilising transcatheter application of the radioactive sources and intraoperative radiotherapy (IORT). All these techniques allow the delivery of higher doses of radiation to regions at risk for harbouring tumour cells while simultaneously sparing many normal tissues at risk for radiation damage. The treatment is usually delivered as a single (IORT) or a few (brachytherapy) radiation fractions, which would not permit visual fractionation, one important aspect of creating a difference in response between normal and tumour tissues [47]. IORT was developed and explored in Japan during the 1970s in patients with various advanced malignancies [48]. Since then, the use of IORT has spread as a treatment modality and is currently employed worldwide in over 250 institutions.

Most of the reports on the use of IORT or brachytherapy, whether alone or (mostly) combined with external chemoradiotherapy, are derived from single institution series. The reports typically include only a few dozen patients, although a recent report included 63 patients collected during a 25-year period [45]. Several of the reports have recently been reviewed in a meeting about "Biliopancreatic malignancy: from gene to cure" held in Amsterdam in February 1999 and published in a supplement of Annals of Oncology (Volume 10, Supplement 4, 1999) [49-51]. With the exception of one trial, no randomised studies exist. A small prospectively randomised trial comprising 26 patients with resected pancreatic adenocarcinomas has been conducted at the National Cancer Institute [52]. In the review of Sindelar and Kinsella [50], updated results were presented on 24 patients. The patients received either IORT (20 Gy) to the resection bed or a standard control treatment. This standard therapy could include postoperative external beam radiotherapy (45–55 Gy) for patients with extrapancreatic extension or nodal disease. Median survival rates of IORT and control patients were 18 and 12 months, respectively, a difference that did not reach statistical significance. Local recurrences occurred in all of the 12 control patients but in only 4 (33%) of the 12 IORT patients.

A group in Amsterdam took a somewhat more pessimistic attitude towards the role of radiotherapy, and in particular intraluminal brachytherapy [53]. This group reported the results of 110 treated patients and concluded that high radiation doses could be dangerous and even detrimental to a positive prognosis. In 38 patients treated with external beam radiotherapy and intraluminal brachytherapy, a median survival rate of 10.5 months was attained. This rate is comparable to 15 other studies using either the same or a similar approach.

Similar to the situation for extrabiliary malignancies, tumours starting in the liver, hepatocellular or cholangiocellular carcinomas, have a dismal prognosis and surgical resection for cure can seldomly be performed [4,54]. Inadequate functional hepatic reserve related to coexistent cirrhosis often precludes surgical resection, sometimes also in comparatively small primaries. There is no evidence that adjuvant protocols will improve treatment results or that systemic treatments are of great benefit [55,56].

Various local tumour destructive methods such as intratumoural ethanol injection [57], radiofrequency ablation [58], cryoablation [59] and stereotactic radiotherapy [60] have been applied. In small tumours (about 2–4 cm) either of these methods can apparently induce complete tumour necrosis and local tumour control can thus be achieved. Since failure at distant sites is not always seen, cure is possible. Whether the chance of cure is similar to that after surgical resection in operable cases is not known. The different modalities have not been compared with each other. This together with a still rather limited experience tells that no scientifically based recommendations can be given favouring one or the other modality in different clinical situations. Practical aspects, complication rates and costs are of relevance in the selection of either of these methods, which basically still must be regarded as experimental.
Selection of patients is paramount

In all treatment situations, the selection of patients most suitable for one or another treatment modality is a determining factor (and self-evident). At present, several treatment modalities, alone or in combination, are possible for patients with locally advanced or inoperable pancreatic and hepatobiliary cancers. These modalities are mainly based on radiation, either as external beam radiotherapy, various brachytherapy modalities, intratumoural injection of radioactivity [61] and IORT and systemic and regional chemotherapy. All of these modalities have been used and results reported, but mainly as a single institution experience. In these studies, selection of the most appropriate patients has been present, and in a way this is how it should be. This has also been the case in the few multicentre trials reported. However, because the selection mechanisms are difficult to judge, most of the apparently favourable treatment results with survival trends for actively treated patients vs. non-treated patients or historical controls must be interpreted with great caution. At present, it cannot be known whether the survival trends are due to patient selection effects or to treatment method. Therefore, properly randomised, sufficiently powered trials are needed to define whether one treatment modality has any effect at all or if it is superior to other modalities. Large, population-based studies in which prospective protocols are carefully followed may provide some evidence of the efficacy of certain treatment protocols, but these studies are probably difficult to perform since the various tumour presentations are relatively uncommon and most treatments are only given at highly specialised referral centres.

References


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