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Overview

Locally Advanced Pancreatic Cancer: The Role of Definitive Chemoradiotherapy

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Abstract

At the time of diagnosis, around 20% of patients with pancreatic cancer present at a resectable stage, 50% have metastatic disease and 30% have locally advanced tumour, non-metastatic but unresectable because of superior mesenteric artery or coeliac encasement. Despite advances in chemoradiotherapy and improved systemic chemotherapeutic agents, patients with locally advanced pancreatic cancer suffer from high rates of distant metastatic failure and from local progression, with a median survival time ranging from 5 to 11 months. In the past 30 years, modest improvements in median survival have been attained for these patients treated by chemoradiotherapy or chemotherapy protocols. The optimal therapy for patients with locally advanced pancreatic carcinoma remains controversial. This review aims to evaluate the role of radiotherapy for these patients.

Key words: Chemoradiotherapy; gemcitabine; locally advanced; pancreatic adenocarcinoma; radiotherapy; review

Statement of Search Strategies and Sources of Information

A search to identify eligible studies was undertaken using the Medline® database (from 1980 to 2013). Additional websites of organisations developing and/or evaluating systematic reviews, meta-analyses and/or therapeutic guidelines, such as the Cochrane Database of Systematic Review and Cancer Care Ontario's Program in Evidence-Based Care, were also consulted. Abstracts of the Proceedings of the Annual Meeting of the American Society of Clinical Oncology, of the American Society of Therapeutic Radiology and Oncology and of the European Society for Radiotherapy and Oncology were searched. The Medline® search was actualised in April 2014. The reference lists of all relevant papers were searched for further studies. This review focused on patients with unresectable locally advanced non-metastatic American Joint Committee on Cancer stage III pancreatic adenocarcinoma. Studies including patients with a previous incomplete resection of the pancreatic tumour and/or having received adjuvant treatment and/or presenting with recurrent disease were excluded. Studies including neuroendocrine pancreatic carcinomas were also excluded. Eligible interventions were external beam radiotherapy and chemoradiotherapy, regardless of the combination scheme (concurrent or sequential) or the modalities (regimen, doses or schedule).

Introduction

Pancreatic carcinoma is one of the leading causes of cancer-related mortality in the Western world. In the UK, 8463 new cases were diagnosed in 2010 and 8320 patients died from this disease in 2011 (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/pancreas). It is estimated that by the year 2020, pancreatic cancer will be the second most common cause of cancer mortality (http://www.pancan.org/). At the time of

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diagnosis, around 20% of pancreatic cancer patients present with a resectable tumour, 30% with a locally advanced tumour and 50% with a metastatic disease [1]. Patients with locally advanced pancreatic cancer (LAPC) comprise a group of patients with an intermediate prognosis between resectable and metastatic patients, with a median overall survival ranging from 5 to 11 months [2]. These patients have pancreatic tumours that are defined as surgically unresectable, but have no evidence of distant metastases. A tumour is considered to be unresectable if it has superior mesenteric artery or coeliac axis encasement of >180 degrees, unreconstructable superior mesenteric vein/portal vein occlusion, aortic involvement or nodal involvement beyond the field of resection (http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf). This patient group needs to be clearly distinguished from patients with borderline resectable tumours, where appropriate neoadjuvant chemotherapy or chemoradiotherapy (CRT) may result in subsequent resectability [3]. Contrary to borderline resectable tumours, patients with LAPC are rarely downstaged and the goal of therapy, like in metastatic disease, is prolongation of survival, symptom palliation and disease control.

The role of radiotherapy in the management of LAPC remains controversial. In the early 1980s, 5-fluorouracil (5-FU)-based concomitant CRT was shown to be better than radiotherapy alone [4]. In the late 1990s, with the introduction of gemcitabine, many countries, including the UK, adopted gemcitabine chemotherapy as the preferred treatment strategy for LAPC, replacing CRT [5]. The results of four randomised trials comparing CRT and chemotherapy were contradictory [6–10]. For these patients, chemotherapy alone or CRT are regarded as acceptable treatment options [11]. More recently, the use of induction chemotherapy to select patients who would probably benefit from CRT has been proposed, but a large randomised trial failed to show an overall survival benefit for this approach over chemotherapy alone [3]. Advanced radiation techniques, including stereotactic body radiotherapy (SBRT) and proton therapy, have shown early promise, but remain investigational.

This aim of this overview is to present the updated evidence and to provide a set of recommendations for the use of radiotherapy in LAPC. Readers are also advised to consult the joint American-French consensus recommendations for a comprehensive review of technical radiotherapy for pancreatic cancer [4].

Treatment Options in the Management of Locally Advanced Pancreatic Cancer

The following treatment approaches have been used in the treatment of LAPC: (i) external beam radiotherapy (EBRT) alone; (ii) upfront CRT (with/without adjuvant chemotherapy); (iii) induction chemotherapy followed by consolidation CRT; (iv) chemotherapy alone. The key clinical trials that have compared these approaches are discussed below.

Upfront Chemoradiotherapy versus External Beam Radiotherapy

Several randomised studies and two meta-analyses have confirmed the superiority of CRT over EBRT in LAPC [12,13]. The meta-analysis reported by Sultana *et al.* included randomised trials only, whereas the Cochrane Collaboration study analysed the randomised trial by Moertel *et al.*, together with historical studies [4]. Sultana *et al.*'s study reported a 31% decrease in tumour-related deaths after CRT. EBRT cannot be recommended as a definitive treatment for LAPC.

Upfront Chemoradiotherapy versus Chemotherapy Alone

CRT was compared with chemotherapy in five randomised trials. Three of these studies were published in the 1980s. Only the GITSG trial (1 year survival 41% versus 19%; $P < 0.02$) showed a survival benefit in favour of CRT [6–8]. Of the more recent randomised trials, the French FFCD-SFRO trial randomised patients to single-agent gemcitabine versus CRT (60 Gy concurrently with cisplatin and 5-FU) followed by maintenance gemcitabine [9]. The overall survival was inferior (8.6 months versus 13 months, $P = 0.03$) and the grade 3–4 toxicity rate was higher in the CRT arm (66% versus 40%, respectively), probably related to the CRT regimen. The ECOG E4201 phase III trial randomised between single-agent gemcitabine and gemcitabine-based CRT (50.4 Gy with concurrent gemcitabine 600 mg/m^2/week) followed by maintenance gemcitabine [10]. The study closed after the inclusion of 74 of the planned 316 patients because of a low accrual rate. The median overall survival was better in the CRT arm (11 months versus 9.2 months, $P = 0.044$). Grade 4 toxicity was more common in the CRT arm (41.2% versus 5.7%, $P < 0.0001$). These results should be considered cautiously because of the limited number of patients included.

A meta-analysis of these studies, including preliminary data from the FFCD-SFRO but not those of ECOG E4201, concluded that the overall survival was not significantly different between CRT and chemotherapy for the treatment of LAPC (hazard ratio = 0.79; 95% confidence interval 0.32–1.95) [12].

Consolidation Chemoradiotherapy versus Chemotherapy or Chemoradiotherapy Alone

CRT (the treatment of local disease) and chemotherapy (the treatment of systemic disease) are complementary treatments and the sequence of chemotherapy followed by CRT may define an optimum therapeutic approach. As 30% of LAPC have occult metastatic disease at diagnosis, induction chemotherapy can help to select a subgroup of patients without early metastatic course who can potentially benefit from locoregional therapy, i.e. CRT. In a phase II trial of 25 patients treated with consolidation CRT after six cycles of fixed-dose rate gemcitabine and low-dose cisplatin, the median survival was 13.5 months for all patients and 17 months for patients who received the two-phase treatment