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.

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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
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/m²/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
downstaging (Table 1). Two important retrospective studies evaluated the role of consolidation CRT in LAPC [15,16]. In the first study, 181 patients received gemcitabine-based induction chemotherapy; 128 patients without tumour progression at the first evaluation received either CRT to a total dose of 55 Gy with 5-FU \(n = 72\) or continued with the same chemotherapy \(n = 56\) [15]. In the final analysis there was significant improvement in the median progression-free survival (10.8 versus 7.4 months) and overall survival (15 versus 11.7 months) in favour of consolidation CRT. The second study compared induction chemotherapy (gemcitabine with/without cisplatin) followed by CRT with CRT alone in 323 patients [16]. Patients who received consolidation CRT had superior survival (11.9 months versus 8.5 months, \(P < 0.001\)). To investigate the role of consolidation CRT, an international phase III trial, LAP07, randomised 442 with LAPC. The first randomisation was between 4 months of induction chemotherapy with gemcitabine versus gemcitabine and erlotinib. The 269 patients who had no tumour progression after 4 months of chemotherapy underwent second randomisation between CRT (54 Gy with concurrent capecitabine 1600 mg/m² bd) or two further cycles of the same chemotherapy. The overall survival was not significantly different in the two arms (15.2 versus 16.4 months, respectively; \(P = 0.8\)) and this study failed to show the superiority of consolidation CRT over chemotherapy alone [17]. The analysis is ongoing to identify a subgroup of patients who might potentially benefit from consolidation CRT. Early data suggest that the use of CRT may improve local control and the chemotherapy-free interval before further treatment is required. Local control is an important end point for therapy as it could translate into quality of life improvement with pain control, prevention of jaundice or gastric outlet obstruction.

**Recommendation**

Systemic therapy should be considered as the mainstay of therapy in LAPC. For patients with stable or responding disease after 3–4 months of chemotherapy, consolidation CRT is an option and may improve local control and delay the onset of retreatment. Where there has been a good partial response from chemotherapy but the tumour remains unresectable, CRT could be considered with a view to downstaging (Table 1).

**The Choice of Systemic Therapy in the Management of Locally Advanced Pancreatic Cancer**

After the introduction of gemcitabine, systemic therapy trials for pancreatic cancer have included patients with both LAPC and metastatic disease [5]. These trials included 15–30% of patients with LAPC and reported an overall survival of 10 months [18,19]. Combination chemotherapy may result in higher response rates (25% versus 8–14%) and progression-free survival, although this does not translate into a survival benefit [20,21]. More recently, successful phase III clinical trials testing FOLFIRINOX (PRODIGE 4/ACCORD 11) and the gemcitabine-nab-paclitaxel combination (MPACT) have focused on the metastatic stage of disease only and have resulted in impressive clinical improvement [22,23]. The encouraging data from these systemic trials and the failure to show overall survival superiority of consolidation CRT in the LAP07 trial have led to a reconsideration of the role of radiotherapy for pancreatic cancer, which was previously ‘mandated’ in the USA. Recent case series of LAPC or borderline resectable pancreatic cancer treated with FOLFIRINOX (5-FU, oxaliplatin, irinotecan, folinic acid) report acceptable toxicity and efficacy profile (Table 2). In many instances, this regimen has been applied as an induction regimen followed by CRT. Marthey et al. recently reported the outcome in 77 LAPC patients from 11 French centres treated with FOLFIRINOX [24]. In this series, 70% had CRT and 36% underwent surgical resection. The 1 year survival reported was 77%. The integration of FOLFIRINOX in the treatment of LAPC will be tested prospectively in a randomised phase II trial (RTOG 1201) evaluating (i) gemcitabine induction followed by conventional CRT (50.4 Gy/28 fractions, concurrent capecitabine); (ii) FOLFIRINOX induction followed by conventional CRT and (iii) gemcitabine induction followed by high-dose CRT (63 Gy/28 fractions, concurrent capecitabine) (Clinicaltrials.gov NCT01921751).

The recent approval of gemcitabine in combination with nab-paclitaxel for metastatic pancreatic cancer has led to the increased use of this regimen in the neoadjuvant setting for borderline resectable or as definitive therapy for LAPC. A retrospective review of 23 patients with borderline resectable \(n = 8\) and unresectable \(n = 15\) LAPC treated with nab-paclitaxel in combination with either gemcitabine or carboplatin reported a radiological partial response in 16/23 (69%) patients [25]. Six patients underwent surgical resection (R0 = 4; R1 = 2). The median survival was 9 months in unresected patients and has not been reached in those undergoing resection. A pilot study in eight patients treated with sequential nab-paclitaxel (two cycles) followed by FOLFIRINOX (two cycles) showed a disease control rate of 100% and downstaging to resectability in 3/8 cases (one of whom had a pathological complete response) [26]. The GAP trial (clinicaltrials.gov NCT02043730), a randomised phase II trial comparing gemcitabine alone or in combination with nab-paclitaxel in LAPC, is due to open shortly in Italy. As yet, no prospective clinical trial has compared gemcitabine-nab-paclitaxel against FOLFIRINOX in the LAPC setting.

**Recommendation**

Gemcitabine-nab-paclitaxel and FOLFIRINOX have both shown overall survival benefit over gemcitabine alone in metastatic pancreatic cancer, and it would be reasonable to consider these regimens as the systemic therapy of choice for LAPC in patients with a good performance status (0–1), pending further phase III trials in the LAPC subgroup (level 3 evidence). Consider gemcitabine monotherapy in performance status 2 patients.
<table>
<thead>
<tr>
<th>Author/year of publication</th>
<th>Treatment</th>
<th>N</th>
<th>Progression free survival (months)</th>
<th>Overall survival (months)</th>
<th>One-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel et al. 1969 (Mayo Clinic) [53]</td>
<td>RT 35−40 Gy</td>
<td>32</td>
<td>6.3</td>
<td>p &lt; 0.05</td>
<td>6*</td>
</tr>
<tr>
<td>Moertel et al. 1981 (GITSG) [4]</td>
<td>CRT 35−40 Gy + 5-FU</td>
<td>35</td>
<td>6.3</td>
<td>p &lt; 0.05</td>
<td>25*</td>
</tr>
<tr>
<td>Moertel et al. 1981 (GITSG) [4]</td>
<td>RT 60 Gy</td>
<td>25</td>
<td>2.9</td>
<td>p &lt; 0.01</td>
<td>7</td>
</tr>
<tr>
<td>Moertel et al. 1981 (GITSG) [4]</td>
<td>CRT 40 Gy + 5-FU then 5-FU</td>
<td>117</td>
<td>8.4</td>
<td>p &lt; 0.01</td>
<td>35</td>
</tr>
<tr>
<td>Moertel et al. 1981 (GITSG) [4]</td>
<td>CRT 60 Gy + 5-FU then 5-FU</td>
<td>111</td>
<td>11.4</td>
<td>p = 0.19</td>
<td>46</td>
</tr>
<tr>
<td>Hazel et al. 1981 [6]</td>
<td>5-FU + methylCCNU</td>
<td>30</td>
<td>7.8</td>
<td>n.s.</td>
<td>7.3</td>
</tr>
<tr>
<td>GITSG 1985 [54]</td>
<td>CRT 60 Gy + 5-FU then 5-FU</td>
<td>73</td>
<td>8.5</td>
<td>n.s.</td>
<td>33</td>
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<td>Klaassen et al. 1985 (ECOG) [7]</td>
<td>CRT 40 Gy + adria then 5-FU</td>
<td>70</td>
<td>7.6</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>GITSG 1988 [8]</td>
<td>CRT 60 Gy + 5-FU then 5-FU</td>
<td>44</td>
<td>8.2</td>
<td>n.s.</td>
<td>32*</td>
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<tr>
<td>Earle et al. 1994 [55]</td>
<td>5-FU</td>
<td>47</td>
<td>8.3</td>
<td>n.s.</td>
<td>26*</td>
</tr>
<tr>
<td>Shinchi et al. 2002 [56]</td>
<td>Best supportive care</td>
<td>31</td>
<td>6.4</td>
<td>p &lt; 0.001</td>
<td>0</td>
</tr>
<tr>
<td>Li et al. 2003</td>
<td>CRT + 5-FU then gem</td>
<td>34</td>
<td>2.7</td>
<td>p = 0.019</td>
<td>6.7</td>
</tr>
<tr>
<td>Chung et al. 2004 [57]</td>
<td>CRT + gem then gem</td>
<td>34</td>
<td>7.1</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Cohen et al. 2005 [58]</td>
<td>CRT 50 Gy + hycanthone</td>
<td>87</td>
<td>7.8</td>
<td>n.s.</td>
<td>7.8</td>
</tr>
<tr>
<td>Chauffert et al. 2008 (FFCD-SFRO) [9]</td>
<td>CRT 50.8 Gy + 5-FU then 5-FU</td>
<td>31</td>
<td>6.4</td>
<td>p &lt; 0.001</td>
<td>13.2</td>
</tr>
<tr>
<td>Loehrer et al. 2008 (ECOG) [10]</td>
<td>CRT 60 Gy + 5-FU + cisplatine then gem</td>
<td>59</td>
<td>8.6</td>
<td>p &lt; 0.03</td>
<td>32</td>
</tr>
<tr>
<td>Mukherjee et al. 2013 [29]</td>
<td>Gem × 7</td>
<td>35</td>
<td>6.1</td>
<td>p = 0.04</td>
<td>9.2</td>
</tr>
<tr>
<td>Mukherjee et al. 2013 [29]</td>
<td>Gem × 5</td>
<td>34</td>
<td>6.3</td>
<td>p = 0.04</td>
<td>11</td>
</tr>
<tr>
<td>Hammel et al. 2013 [17]</td>
<td>gem-cape/CRT 50.4 Gy + cape</td>
<td>136</td>
<td>11.8</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>Abbreviations: N, number of patients; GISTG, Gastrointestinal Study Group; ECOG, Eastern Cooperative Oncology Group; RT, radiation therapy; CRT, chemoradiation; 5-FU, 5-fluorouracil; SMF, streptozocin, mitomycin-C, and 5-flouracil; gem, gemcitabine; doxi, doxifluoridine; mito C, mitomycine C; cape, capecitabine.</td>
<td></td>
<td></td>
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<td>* Extrapolated from survival curve.</td>
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</table>
The Choice of Radiosensitising Chemotherapy

Numerous chemotherapy agents/combinations have been used as radiosensitisers in LAPC: fluoropyrimidines (5-FU, capecitabine), cisplatin, mitomycin, gemcitabine, oxaliplatin, paclitaxel, docetaxel and tyrosine kinase inhibitors. Concurrent fluoropyrimidines and gemcitabine are the commonly used regimens.

Fluoropyrimidines versus Gemcitabine as Radiosensitisers

5-FU and more recently its oral pro-drug, capecitabine, have been the traditional radiosensitisers in the management of gastrointestinal cancers [4,27]. Given its potent radiosensitisising properties and systemic cytotoxic effects, over 30 studies have investigated the activity of gemcitabine as a radiosensitiser. However, a wide range of gemcitabine doses (200–1000 mg/m²), schedules (weekly versus bi-weekly), radiotherapy dose-fractionation and radiation field (involved field versus prophylactic nodal radiation) makes it difficult to draw any firm conclusions as to what could be considered as an optimal gemcitabine-based CRT schedule.

Five studies (four randomised controlled trials and one retrospective review) have compared 5-FU-based CRT with gemcitabine-based CRT. These studies have used a 'radio-sensitisising' dose of gemcitabine (250–600 mg/m²). A meta-analysis of four of these studies (n = 229) has shown a benefit for gemcitabine-based CRT (12 month survival rate relative risk 1.54, P = 0.03) but at the expense of severe acute haematological toxicities [28]. The fifth study, the largest randomised phase II trial comparing gemcitabine versus fluoropyrimidine radiation (SCALOP), compared radiotherapy combined with capcitabine (830 mg/m² twice daily) or gemcitabine (300 mg/m²/week) in 74 patients without tumour progression after 12 weeks of induction therapy with gemcitabine and capecitabine [29].

Full-dose gemcitabine in conjunction with radiation has been tested in several single arm trials, with promising results. McGinn et al. conducted a phase I dose escalation study and reported a maximum tolerated dose of 36 Gy/15 fractions in combination with full-dose gemcitabine [30]. At least two phase II trials have subsequently tested this regimen. A median survival of 11.2 months and a 1 year freedom from local failure rate of 64% with acceptable grade 3 gastrointestinal toxicity (22%) was reported in 74 patients with LAPC [31]. Small et al. treated 39 patients (LAPC = 14, borderline resectable = 9, resectable = 16) and reported a 1 year overall survival of 73% for the entire cohort and 47% for the LAPC cohort. A retrospective study by Huang et al. compared patients treated with 5-FU-based CRT with full-dose gemcitabine-based CRT [32]. Overall survival favoured the gemcitabine-CRT group, and raises the possibility that the lower dose of gemcitabine may have led to the survival detriment seen in the gemcitabine-CRT arm of the SCALOP trial. Radiotherapy dose intensification with IMRT alongside full-dose fixed-dose rate gemcitabine was reported by Schipper et al. [33]. At the recommended phase II dose of 55 Gy/25 fractions, the probability of dose-limiting toxicity was 0.24. The median and 2 year overall survival were reported as 15 months and 30%, respectively, showing feasibility and promising activity for a chemo- and radiotherapy-intensified regimen.

Molecular Targeted Therapies in Combination with Radiation

Despite advancement in radiation techniques, conventional CRT regimens result in a local control rate of around 50%, potential downstaging occurs in only a third of the patients and a pathological complete response is seen in <5% of patients [31,34,35]. As the biological basis of cancer is better understood, the use of cancer-specific therapies is being increasingly investigated to target tumour signalling, or for modulation of the tumour micro-environment, including hypoxia and vascularity. Targeting the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) receptor pathways in conjunction with CRT has been investigated. A phase I study from Brown University reported a maximum tolerated dose of 50 mg erlotinib, in combination with gemcitabine, paclitaxel and radiotherapy (50.4 Gy), with a median survival of 14 months [36]. Another phase I study combining erlotinib (100 mg daily), gemcitabine 40 mg/m² biweekly and EBRT (50.4 Gy) reported a median survival of 18.7 months [37]. The EGFR inhibitor, cetuximab, in combination with gemcitabine and radiotherapy has been assessed in a phase I study and reported only 9% grade 3–4 toxicities and a median overall survival of 10.5 months [38]. A subsequent phase II trial

Table 2

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Radiation (number of patients)</th>
<th>Response rate</th>
<th>R0 resection (number of patients)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boone et al. [59]</td>
<td>25</td>
<td>12</td>
<td>NR</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Conroy et al. [60]</td>
<td>11</td>
<td>0</td>
<td>27%</td>
<td>0</td>
<td>Overall survival 15.7 months</td>
</tr>
<tr>
<td>Faris et al. [61]</td>
<td>22</td>
<td>22</td>
<td>27%</td>
<td>5</td>
<td>Progression-free survival 11.7 months</td>
</tr>
<tr>
<td>Hosein et al. [62]</td>
<td>18</td>
<td>3</td>
<td>NR</td>
<td>8</td>
<td>1 year progression-free survival 83%</td>
</tr>
</tbody>
</table>

NR, not reported.
from the MD Anderson Cancer Centre assessed the efficacy and safety of induction cetuximab, gemcitabine and oxaliplatin followed by cetuximab and capecitabine in combination with EBRT [39]. The median overall survival was 19.2 months in this selected population. Acneiform rash correlated with improved survival ($P = 0.001$), suggesting an activity of cetuximab in a subgroup of patients.

Preclinical data have shown that inhibition of VEGF has radiosensitising effects that could be related to enhanced lethality of tumour cells or normalisation of tumour vasculature leading to a reduction in tumour hypoxia [56]. A phase I study from the MD Anderson Cancer Centre using the combination of bevacizumab, capecitabine and radiation (50.4 Gy) followed by maintenance treatment with bevacizumab reported three tumour-associated bleeding duodenal ulcers and one duodenal perforation among the first 30 patients [40]. No additional bleeding events occurred among the final 18 patients after patients with duodenal involvement were excluded. A subsequent phase II using the same regimen reported a median survival of 11.9 months and 35.4% grade 3 or greater treatment-related gastrointestinal toxicity [41].

Many molecular abnormalities have been implicated in contributing to the development of pancreatic cancer. Among them, four tumour suppressor genes have been implicated (p16, p53, DPC4 and BRCA2), with incidences of 50–95% in all pancreatic tumours. Among oncogenes, K-ras activation is observed in 90% of these tumours. EGFR and KRAS signalling is mediated, in part, through the PI3 kinase/Ark signalling pathway, and preclinical data suggest that P13K inhibition through the HIV protease inhibitor, nelfinavir, may lead to radiosensitisation [42–44]. In a phase I trial, 12 patients with LAPC were treated with gemcitabine/cisplatin-based CRT (59.4 Gy/33 fractions), in combination with nelfinavir [45]. Grade 3/4 non-haematological toxicity was acceptable (16.7%); a complete FDG-PET response was seen in 50% of patients and R0 resection was achieved in six patients. The median overall survival was 18 months. In addition to this study, a recently reported phase I study combined radical CRT with nelfinavir in stage IIIA and B non-small cell lung cancer showed minimal toxicity with 5/9 complete responses [46]. This promising agent will now be investigated in the UK in a randomised phase II trial (SCALOP2) where after induction chemotherapy with gemcitabine and nab-paclitaxel, patients with stable/responding disease will be randomised to (i) continuing same chemotherapy; (ii) conventional CRT (50.4 Gy/28 fractions concurrent with capecitabine); (iii) conventional CRT with nelfinavir; (iv) high-dose CRT (60 Gy/30 fractions concurrent with capecitabine); (v) high-dose CRT with nelfinavir. This trial is funded by Cancer Research UK and will open later in the year (Clinicaltrials.gov NCT02024009).

**Recommendation**

Capecitabine is the preferred radiosensitiser in LAPC. The role of full-dose gemcitabine in combination with radiation remains investigational. Research should focus on investigating novel radiosensitisers exploiting tumour biology, tumour–stromal interaction, hypoxia and tumour vascularity.

**Modern Radiation Techniques**

A full review of SBRT for pancreatic cancer is beyond the scope of this paper, and has been reviewed elsewhere [47]. Recent trends have used SBRT as a sandwich treatment in between chemotherapy cycles, or as a consolidative regimen after induction chemotherapy [48]. There is also an increasing trend to use three to five fraction regimens rather than the single fraction treatment reported during the early days of pancreatic SBRT [49]. Gurka et al. reported the results from a pilot study of gemcitabine given at a dose of 1000 m2/week on weeks 1–3 of a 4 week cycle for six cycles, with SBRT (25 Gy/five consecutive fractions) during week 4 of cycle 1 [50]. Eleven patients were enrolled, there were no grade 3 or higher radiation-related toxicities, progression-free survival and overall survival were 6.8 and 12.2 months, respectively. Recently, Chuong et al. reported the outcome of a novel dose-painting five-fraction SBRT technique whereby the tumour received a median dose of 25 Gy and areas of vessel abutment (away from the organs at risk) received a median dose of 35 Gy [51]. All patients received induction chemotherapy. Seventy-three patients (borderline resectable $= 22$; LAPC $= 41$) were treated, 31/32 borderline resectable tumours undertook R0 resection and a median overall survival of 16.4 month and 15 months was reported in the borderline resectable and LAPC subsets, respectively.

**Customising Therapy: Selection of Patients/Therapy Through Molecular Markers**

The molecular marker DPC4 has been shown to predict for local versus distant progression in an autopsy series and in a prospective single-arm clinical trial [39,52]. In both of these studies, individuals with intact DPC4 had a lower risk of distant spread, and this could therefore be a potential marker to identify patients who would probably benefit from (intensified) local therapy and those who should be treated with chemotherapy alone. Similarly, the combination of EBRT with PARP inhibitors in BRCA 1/2 mutant tumours or PTEN loss, and with ATR inhibitors in tumours with ATM loss may further maximise the chances of tumour response.

**Conclusions**

The treatment of LAPC is one of the most formidable challenges that clinical and translational researchers face today. In the last 30 years, little progress had been made despite numerous trials. The results of the LAP07 and the other trials and meta-analyses quoted above do not support the unselective use of conventional CRT for LAPC over chemotherapy alone, although it may be used as a consolidative regimen after induction chemotherapy. Biological
selection of patients with truly localised disease through molecular markers like DPC4, the development of new targeted therapies through a better understanding of pancreatic carcinogenesis and radio-resistance and the rapid evolution in modern radiation techniques may as yet define a niche role for CRT in this disease site. Modern day CRT trials like LAP07 and SCALOP suggest that CRT is an active, well-tolerated regimen, and future efforts should be directed at building on this platform by improving both the systemic and the radiation components of treatment.

Acknowledgement

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References


