Adjuvant chemoradiotherapy for high-risk pancreatic cancer

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ABSTRACT

Introduction: The role of adjuvant chemoradiotherapy for resected pancreatic cancer remains controversial. Several trials have failed to draw firm conclusions. The risk of local and metastatic relapse remains high after radical surgery. This is a single institutional review, evaluating the outcomes of patients with high-risk resected pancreatic cancer and treated with adjuvant chemoradiotherapy.

Methods: A retrospective review was conducted on 18 consecutive patients with pancreatic cancer and treated with adjuvant chemoradiotherapy at the Department of Radiation Oncology, National Cancer Centre, Singapore, between January 2000 and December 2004. 56 percent were women. The mean age was 61.5 (range 50–73) years. Patients had either AJCC 2002 Stage I (17 percent), Stage II (11 percent), Stage III (22 percent) or Stage IVA (50 percent). The median radiation dose delivered was 5,400 (range 4,140–5,500) cGy using 180 cGy fractions. Concurrent chemotherapy was administered with 5-fluorouracil (56 percent), gemcitabine (28 percent) or capacetabine (17 percent).

Results: The median follow-up of patients still alive at the time of analysis was 48 months. Metastatic disease had developed in 13 patients. Two patients had local recurrence within the radiation field. The median survival of the cohort is 21.6 (range 8.5–62.7) months. One-year survival is 89 percent, 2-year survival 39 percent and 3-year survival 28 percent.

Conclusion: The data supports the use of adjuvant chemoradiotherapy for high-risk pancreatic cancer. Our results are comparable to published data from similar studies. Although radiotherapy is effective in reducing local failure, effective systemic treatment is also essential.

Keywords: adjuvant chemoradiotherapy, chemoradiotherapy, pancreatic cancer, resected pancreatic cancer

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INTRODUCTION

Pancreatic cancer remains one of the top five causes of death in the Western world. While surgery remains the only curative single modality treatment, only 10%–25% of patients present with disease amendable to resection, with a median survival of 10–20 months and a five-year survival of 11%–25% after surgery.[1] Most failures occur within 1–2 years after surgery, with high rates of local recurrence, intra-abdominal failure and hepatic metastases.[2] Favourable subsets include patients with resected tumours measuring less than 3 cm, negative nodal status and microscopically negative surgical margins.[3] The role of adjuvant chemoradiotherapy for resected pancreatic cancer remains questionable. While adjuvant treatment may improve survival, recent randomised studies have been inconclusive as to which modality is the most appropriate.

In North America, adjuvant chemoradiotherapy was adopted as the standard approach in patients with resected pancreatic adenocarcinoma, based on the positive results of a Gastrointestinal Tumor Study Group (GITSG) trial using split course radiotherapy with concurrent 5-fluorouracil bolus administration.[4] This trial was terminated prematurely due to poor accrual, but more importantly, an increasingly large survival difference was observed, in favour of the adjuvant chemoradiotherapy arm (median survival 20 vs. 11 months; p = 0.03). A further non-randomised addition of 30 patients to the adjuvant treatment arm yielded similar results.[5]

In contrast, a European Organisation for Research and Treatment in Cancer (EORTC) study only found a trend towards longer median survival in patients who had resected pancreatic cancer and received adjuvant chemoradiotherapy, as compared with those who had surgery alone (17 months vs. 12.6 months).[6] A recent study by the European Study Group for Pancreatic Cancer (ESPAC-1), being the largest randomised adjuvant trial, showed a significant survival benefit in patients receiving

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Table I. Various chemotherapy regimens used.

Chemotherapy	Chemoradiotherapy phase	Adjuvant phase
5-fluorouracil/folinic acid bolus 4-weekly	400 mg/m^2 D1–4 and last 3 days of RT (5) or 350 mg/m^2 D1–5 and last 5 days of RT (1)	425 mg/m^2 D1–5, 4-weekly (2)
5-fluorouracil continuous infusion	200–225 mg/m^2 daily (4)	NA
Capecitabine	650–825* mg/m^2 twice daily (3)	1,000 mg/m^2 twice daily (1)
Gemcitabine	50–80 mg/m^2 biweekly (3) 160–300 mg/m^2 weekly (2)	1,000 mg/m^2 D1,8,15 4–weekly (5)

* Capecitabine dose for patients taken 5 days weekly with concurrent radiotherapy
Numbers in parenthesis represent the number of patients treated with the drug.

adjuvant chemotherapy while adjuvant chemoradiotherapy had a deleterious effect on survival.[7] The results from this trial formed the basis for the use of adjuvant chemotherapy as the standard treatment across many centres in Europe and worldwide. The results of a subsequent meta-analysis in which patients from the ESPAC-1 trial formed a large proportion of the cohort, showed a 25% reduction in the risk of death (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.64–0.90, p = 0.001) in patients receiving adjuvant chemotherapy, and no significant difference in survival for patients receiving adjuvant chemoradiotherapy (HR 1.09; 95% CI 0.89–1.32; p = 0.43).[8] Only the subgroup with a margin-positive disease showed a trend towards improved survival with adjuvant chemoradiotherapy.

In Singapore, pancreatic cancer constituted 2% of all cancers diagnosed in males and females between 1998 and 2002. The age-standardised incidence rates have increased in parallel for both genders over the last 35 years. There are about 150 cases a year, with an incidence of 5.0 per 100,000 for males and 3.6 per 100,000 for females.[9] Many patients present in the advanced stages of the disease. Resectable cases remain few in number. Only patients deemed to have a high risk of relapse are considered for adjuvant chemoradiotherapy. The purpose of this study was to present the outcomes of patients with high-risk resected pancreatic cancer, treated with adjuvant chemoradiotherapy, at the National Cancer Centre, Singapore.

METHODS

This is a retrospective study approved by the Institutional Review Board of the National Cancer Centre, Singapore. A cohort of 18 consecutive patients, treated with adjuvant chemoradiotherapy at the Department of Radiation Oncology from January 2000 to December 2004, were enrolled for this study. All patients had undergone curative surgical resection of the primary pancreatic tumour, regional lymph nodes and involved adjacent structures. The majority of these patients referred for adjuvant chemoradiotherapy had high-risk factors, such as positive or close margins, locally-invasive tumours or presence of regional nodal disease. Various chemotherapy regimes were used during the combined treatment phase, as shown in Table I. The majority of patients were administered concurrent 5-fluorouracil based chemotherapy. In recent years, medical oncologists favoured using capecitabine for its oral formulation, and gemcitabine for the reported higher response rate and clinical benefit rate when used in patients with advanced pancreatic cancer.[10] Treatment started with concurrent chemoradiotherapy for all patients. Only eight patients continued to have adjuvant chemotherapy after that. The decision as to which chemotherapeutic agent was employed, depended on the medical oncologists as well as the patient performance status. Dose modifications were individualised, with 20% dose reductions after reported major toxicities.

Radiotherapy was planned and delivered in two phases. The first phase consisted of a total dose of 4,500 cGy, delivered in 25 fractions of 180 cGy each, to the tumour bed and regional lymphatics, by a linear accelerator with 10 mV photon beams. A boost dose of 900–1,000 cGy was administered following the first phase to the tumour bed, for patients with positive or close surgical margins. The clinical target volume (CTV) was delineated on planning computed tomography (CT) images with CT simulation software. The initial CTV comprised the previously-resected tumour volume as defined by the preoperative scan, with appropriate margins and the regional lymphatics. For tumours located in the proximal pancreas, the CTV included the porta hepatitis and retroperitoneal para-aortic lymphatic vessels between the coeliac axis and superior mesenteric artery to the anterior level of the vertebral bodies. The duodenal stump and the distal pancreatic stump were also included in cases with inadequate resection margins. The CTV was uniformly expanded by 1 cm to form the planning target

Table II. Characteristics of eligible patients (n = 18).

	No. (%)
Gender	
Male	8 (44)
Female	10 (56)
Tumour location	
Head	6 (33)
Uncinate	2 (11)
Body	6 (33)
Tail	4 (22)
AJCC stage	
I	3 (17)
II	2 (11)
III	4 (22)
IVA	9 (50)
Lymph node	
Negative	11 (61)
Positive	7 (39)
Resection margins	
Negative	4 (22)
Positive	7 (39)
Close (< 10 mm)	7 (39)

AJCC: American Joint Committee on Cancer

Table III. Various radiation dose regimens used.

Radiation dose (cGy)	No. (%)
< 4,500	1 (6)
4,500/25#	2 (11)
5,040/28#	2 (11)
4,500/25# + 900/5# boost	10 (56)
4,500/25# + 1,000/5# boost	3 (17)

#: fractions

volume (PTV). The boost dose was applied to the volume of the resected tumour with a 2-cm margin. A three-field treatment technique was used for all cases, with a single anterior and two lateral fields. Optimised treatment plans were produced for both the PTV and boost volume in accordance with ICRU 50/62 recommendations. Coverage of the PTV was considered to be adequate if at least 95% of PTV received at least 95% of the prescription dose. Dose-volume histograms were obtained for the target volumes and organs at risk, viz. liver, kidneys and spinal cord. The prescribed dose is 4,500 cGy to the regional lymphatics, 5,040 cGy to the tumour bed with clear margins and 5,400 cGy to the tumour bed with positive or close margins.

Before starting adjuvant combined treatment, full staging investigations were performed to detect any recurrence or progression of disease. This included CT of the chest, abdomen and pelvis. Magnetic resonance imaging and fluorine-18 fluorodeoxyglucose positron emission tomography were only performed when indicated and not as a routine. During the entire treatment period, clinical reviews and physical examinations were performed weekly by the radiation oncologists. Blood analyses were performed prior to administration of each cycle of chemotherapy or on a three-weekly basis for the oral and infusional regimes. Adverse effects were assessed with the use of the common toxicity criteria (CTC version 2.0).[11] After completion of the adjuvant treatment, all patients were reviewed at three-monthly intervals. Blood investigations and serum CA19-9 levels were routinely recorded at each review. Surveillance chest radiographs and abdominal CT were performed three months after completion of the adjuvant therapy. This was followed by repeat scans on a six-monthly basis or as clinically indicated.

The primary endpoint of the study was the three-year survival rate. Secondary endpoints were time to disease progression and rates of disease recurrence. Survival was calculated from the date of surgical resection until the date of death from any cause. The date of disease recurrence was recorded as the date of radiological detection of the disease, with the time to progression recorded from the last day of the adjuvant treatment. For patients lost to follow-up, the data was censored on the date the patient was last seen alive. Survival estimates were derived by the Kaplan-Meier method.

RESULTS

Of the 18 patients, 56 percent were women and the mean age was 61.5 (range 50–73) years. The ethnic distribution of our patients was as follows: Chinese (83%), Malays (11%) and Indians (6%). All the patients had either AJCC 2002 Stage I (17%), Stage II (11%), Stage III (22%) or Stage IVA (50%) disease.[12] Lymph nodal involvement was found in seven patients (39%). Seven patients had positive margins, while another seven had close margins of < 10 mm. Of the three patients with Stage I disease, two had positive resection margins, while the third had a margin of 1 mm. These three patients were treated with adjuvant chemoradiotherapy as they were deemed to have a high risk of local relapse due to their margin status. The pretreatment patient characteristics are shown in Table II.

Radical surgery was performed for all 18 patients. An analysis of the nine patients who had T4 (Stage IVA) disease and underwent radical surgery, showed T4N0 disease in six patients and T4N1 disease in the remaining three. Radical surgery was feasible in the majority, by virtue of the extent of T4 disease being splenic invasion in two patients and splenic vein involvement in another four. These structures were resected with the primary tumour. The remaining three patients underwent radical surgery despite vascular involvement found on laparotomy. The primary tumours were initially deemed to be resectable by their respective surgeons. All patients were treated with conformal radiotherapy. Radiation was delivered using 10 MV photons

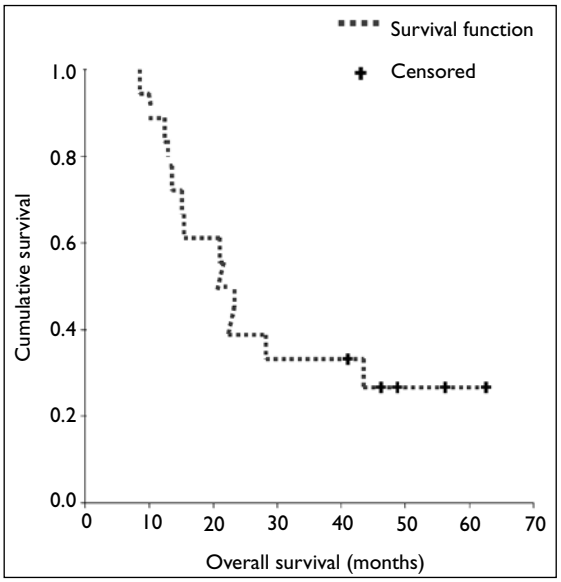

Fig. 1 Kaplan-Meier graph shows overall survival for all enrolled patients.

to the tumour bed and locoregional lymphatics. The median dose was 4,500 cGy to the regional lymphatics and 5,400 (range 4,140–5,500) cGy to the tumour bed. Table III lists the various treatment doses delivered.

17 patients (94%) completed the planned radiotherapy treatments. Treatment was halted at 4,140 cGy for one patient who suffered from grade 3 mucositis and diarrhoea, a likely consequence of the 5-fluorouracil chemotherapy used. This patient had close resection margins. A four-day radiotherapy treatment break was necessary for another patient who was hospitalised for neutropenic sepsis. This was followed by a 20% dose reduction for her subsequent chemotherapy. Otherwise, adverse reactions during concurrent chemoradiotherapy were well tolerated. Majority was of CTC grades 1 and 2, with anorexia (61%), nausea and emesis (33%) and weight loss (61%) in the range 0.5–4 kg, all less than 10% of the pretreatment body weight.

Concurrent chemotherapy was given in the form of 5-fluorouracil (56%), gemcitabine (28%) or capecitabine (17%). Only eight patients (45%) continued to receive further adjuvant chemotherapy, completing 3–6 more cycles. Three patients continued to receive adjuvant gemcitabine from the initial five, while two patients were converted from capecitabine to gemcitabine. Two patients continued with bolus 5-fluorouracil infusions and the last patient capecitabine. The various dose regimens are shown in Table I. Ten patients did not proceed with adjuvant chemotherapy. Reasons include persistent neutropenia in two patients, poor tolerance of acute toxicity and poor performance status after completion of chemoradiotherapy in five patients. One patient stopped

Table IV. Sites of first recurrence.

Organ site	No. of patients	Proportion of patients with recurrence (%)
Liver	11	85
Peritoneum (carcinomatosis)	4	31
Pulmonary	1	8
Pancreas/ regional nodes	2	15
Non-regional nodes	3	23

adjuvant chemoradiotherapy due to grade 3 mucositis and diarrhoea as previously mentioned and for the last two patients, no specific reasons were stated. Adverse effects from chemotherapy included poor tolerance (39%) and neutropenia (33%). Two patients who received gemcitabine had neutropenic sepsis and one patient developed line sepsis while receiving infusional 5-fluorouracil. Patients receiving the Mayo-type 5-fluorouracil bolus infusions reported more mucositis (11%) and diarrhoea (11%).

The median follow-up period was 48 months for all surviving patients. Death had occurred in 13 (72%) patients during the follow-up period, all due to metastatic disease progression except for one who died from complications related to a cerebrovascular event. There was no evidence of metastatic disease at the time of her death. This number included one patient lost to follow-up after 22 months, presumed to have succumbed to metastatic disease as she declined treatment for rapidly progressing liver metastases, which developed nine months after completion of adjuvant therapy. Recurrent disease developed in 13 patients, within a median time of seven (range 1–56) months after completion of adjuvant treatment. 85% of patients relapsed in the liver, 31% in the peritoneum, 23% intra-abdominal lymph nodes and 8% in the lung (Table IV). Only two patients had local recurrence within the radiation field, both synchronously with liver metastases.

Among the eight patients who received further adjuvant chemotherapy after concurrent chemoradiotherapy, six patients relapsed, with a median time to disease progression of eight (range 1–24) months. The two remaining patients in this group were still free of disease recurrence at the time of reporting. All three patients with stage I disease are alive after a median follow-up of 56 (range 41–62.7) months. One patient in this group developed a solitary liver metastasis in segment VIII of the liver, 56 months after primary surgery. This was treated with radiofrequency ablation. The patient remained disease-free at the time of reporting, six months post-procedure. The median survival for all 18 patients was 21.6 (range 8.5–62.7) months. The one-year survival was 88%, two-year survival 39%, and three-year survival 28%. (Fig.1).

DISCUSSION

The outcomes of our patients with high-risk resected pancreatic cancer treated with adjuvant chemoradiotherapy appear to be promising, with a median survival of 21.6 months within the cohort. This is despite a relatively high risk of local and systemic recurrence from advanced T3–T4 disease, node positive disease and/or positive resection margins. These initial results are also comparable to previously-published data from the GITSG series. In our study, two patients (11%) recurred locally, significantly lower that the 35% overall local recurrence rate for patients with T3–T4 and/or node-positive quoted in the ESPAC-1 study.[7] The EORTC study also reflected locoregional relapse rates of 34%–37% in both the observation and treatment arms, either alone or as a component of failure.[6] The use of split-course radiotherapy in these prior studies is not favoured by most radiation oncologists in this modern era due to radiobiological disadvantages. The low local relapse rate in our study may be due to the higher dose of radiation delivered to the area at risk, with median doses of 54 Gy. The better local control could also be attributed to the additive effect of concurrent radiosensitisation, bringing the biological doses even higher. There is, however, no conclusive evidence of survival benefit of radiation dose escalation in the adjuvant setting.[13] Similarly, radiation doses have been escalated to 64.8 Gy with minimal toxicity and comparable three-year survival of 21%.[14] Toxicity, though a concern, has been well tolerated and acceptable. With the advent of planned radiation fields using intensity-modulated radiation therapy, there is potential to significantly improve radiation therapy of pancreatic cancers by reducing normal tissue doses, and simultaneously allowing dose escalation to enhance locoregional control.[15,16]

Given the diverse chemotherapy regimes used in our study, it is difficult to assess the efficacy of the various radiosensitising chemotherapy used. Survival benefits have been reported to be similar in patients with locally-advanced pancreatic cancer and who received either concurrent gemcitabine or infusional 5-fluorouracil. Patients who underwent successful surgical resection after significant downstaging with concurrent gemcitabine chemoradiotherapy, had a higher margin-negative resection rate, but also a higher rate of severe toxicity as well. It is also prudent to note that in this study, patients whose treatments had been complicated by neutropenic sepsis, received either concurrent or adjuvant gemcitabine. The possible benefits and the high rates of toxicity could define a very narrow therapeutic index for concurrent gemcitabine-based chemoradiotherapy compared to 5-fluorouracil.[17] Nevertheless, there is a need to assess modern radiotherapy combined with newer and more active drugs that have the potential to maximise cell radiosensitisation and to treat metastatic disease. Gemcitabine has emerged as a standard of care in advanced pancreatic cancer. It possesses potent radiosensitising properties and has been used with concomitant radiation in locally-advanced pancreatic cancer.[18] Recent Phase II trials using concurrent gemcitabine with radiation in the adjuvant setting have demonstrated acceptable local control and survival results.[19,20]

Despite superior local control with higher radiation doses, the problem lies with metastatic disease progression. Overall, 72% of patients in this study subsequently progressed despite adjuvant treatment. The earliest recurrence came within a month after completion of the adjuvant treatment. Almost all recurrences occurred within a year, with distant disease manifesting in half of these patients within seven months of completing adjuvant chemoradiotherapy and/or chemotherapy, with the exception of one patient who developed a solitary liver metastasis 56 months after primary surgery. This patient was one of the three patients with Stage I disease. None of them recurred locally despite concerns with resection margins. However, even patients with early disease are at risk of subsequent metastatic dissemination. Therefore, the benefit of adjuvant chemotherapy for early disease cannot be ruled out as well. In the ESPAC-1 study, the median time to recurrence was 10.7 (95% CI 8.8–15.5) months among patients who received adjuvant chemoradiotherapy, with a superior result in patients who received adjuvant chemotherapy instead. Naturally, the radiosensitising dose of any chemotherapeutic agent given concurrently with radiotherapy is considered ineffective in eradicating systemic disease. In accordance to the ESPAC-1 data, one could consider offering adjuvant chemotherapy as a reasonable approach. Recent updates from the Radiation Therapy Oncology Group have also suggested the benefit of adjuvant chemotherapy previously reported in ESPAC-1, with an advantage of adjuvant gemcitabine over 5-fluorouracil given after adjuvant chemoradiotherapy.

Increasingly, the use of adjuvant chemotherapy has replaced chemoradiotherapy after the publication of the ESPAC-1 study. It will certainly be useful to compare the outcome of our local patients treated in accordance to the different arms of this study. The value of radiotherapy, however, cannot be discounted, especially for patients with a high risk of local relapse. One approach to optimise the benefit of systemic therapy is to administer chemotherapy first and then interject the treatment with

concurrent radiotherapy. The combination of radiation and chemotherapy does come with significant toxicity. It is difficult to combine full-dose chemotherapy with locoregional treatment, and the trials that have managed this usually limit the radiation doses or compromise on the treatment fields, as demonstrated in patients with locally-advanced pancreatic cancer.[21] Nevertheless, concurrent chemoradiotherapy has been effective in reducing the local recurrence for our group of patients, many of whom progress with metastatic disease. The current practice at the National Cancer Centre is for all cases with resected pancreatic cancer to be discussed at a multidisciplinary meeting. All patients with high-risk histopathological indications, such as large tumours, lymph nodal involvement and positive or close resection margins, are considered for adjuvant chemoradiotherapy, but only after a full disclosure of the uncertainties and controversies of the current management, and with the knowledge that perhaps future studies may shed more light in this area.

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