Use of chemotherapy and radiotherapy in patients with pancreatic cancer in Victoria (2002–2003): a retrospective cohort study

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ABSTRACT

Objective: To describe the management and outcomes of a population-based cohort of patients with pancreatic cancer treated with chemotherapy or radiotherapy in Victoria, Australia.

Design, setting and patients: Questionnaire-based study of patients diagnosed with pancreatic cancer during 2002–2003 in Victoria who were retrospectively identified from the Victorian Cancer Registry and followed up for a minimum of 5 years.

Main outcome measures: Reported treatment, referral patterns and survival rates.

Results: 1044 patients with pancreatic cancer were identified, of whom 927 were eligible for the study. Completed questionnaires were obtained for 831 eligible patients (response rate, 89.6%) and data for 66 patients with tumours of the ampulla of Vater and neuroendocrine tumours were excluded. Of the remaining 765 patients, 6.5% were managed in multimodality clinics. Chemotherapy was considered for 413 patients and radiotherapy was considered for 162. One-third of the cohort (275 patients) received chemotherapy, most commonly as palliative treatment (185). Single-agent gemcitabine was the most common palliative treatment (154), and was associated with a median overall survival of 6.6 months. Radiotherapy was used in 119 patients (15.6% of the cohort) — it was used alone or with chemotherapy, as postoperative adjuvant treatment, as potentially curative radical treatment, or as palliative treatment. For 45 patients with locally advanced disease who were treated with chemoradiation as radical treatment, median overall survival was 13.1 months.

Conclusions: There appears to be under-referral of patients to medical and radiation oncologists. Median survival of patients treated with radical chemoradiation or palliative chemotherapy is consistent with clinical trial data, but outcomes for patients in our cohort were generally poor. Development and implementation of treatment guidelines may result in improved outcomes.

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Pancreatic cancer represents 2% of all cancers, but accounts for 5% of all cancer deaths.[1] In Victoria during 2006, 580 new cases were diagnosed and 529 people died from pancreatic cancer.[1] Median survival after diagnosis is around 3 to 6 months.[1,2] Five-year survival is less than 5% and has improved only slightly over the past 20 years.[2] Surgery is the only curative treatment and results in long-term survival of less than 20%.[3,4] However, most patients present with unresectable disease and many experience rapid clinical deterioration. This has not changed over several decades.[5,6]

Small trials have shown that survival in patients with locally advanced but unresectable disease may be improved using a combination of chemotherapy and radiotherapy, rather than radiotherapy alone.[7-9] Various studies of chemotherapy and radiotherapy suggest that adjuvant therapy may improve outcomes for patients after surgery.[10-15] Most patients with pancreatic cancer will develop metastases and are potential candidates for treatment with systemic chemotherapy, which may result in clinical benefit and is associated with a small survival advantage.[16]

The Victorian Cooperative Oncology Group, in collaboration with the Victorian Cancer Registry (VCR) — a population-based cancer registry that covers Victoria, Australia — undertook to examine patterns of care for patients diagnosed with pancreatic cancer over a 2-year period. Here, we describe the use of chemotherapy and radiotherapy in these patients, and outcomes of treatment.

METHODS

Patients diagnosed with pancreatic cancer during 2002–2003 were identified from the VCR. Primary questionnaires were sent to treating doctors to confirm each patient's eligibility and collect details of each patient's management; these included questions about presentation (referral source, symptoms, performance status, and diagnostic and staging investigations), treatment intent, and interventional and surgical procedures. These results will be reported elsewhere at a later date.

Supplementary questionnaires requesting specific treatment details were sent to medical and radiation oncologists for patients referred for chemotherapy or radiotherapy. These included questions about referral source, treatment intent, details of radiotherapy planning and delivery, and ongoing follow-up. Here we report on these results. Patients were followed up until the end of 2008 (to provide a minimum follow-up period of 5 years) using mortality data from the Victorian Registry of Births, Deaths and Marriages and the National Death Index.

Descriptive statistics were analysed using SPSS 14.0, release 14.0.2 (SPSS, Chicago, Ill, USA).

Ethics approval was obtained from the Cancer Council Victoria Human Research Ethics Committee.

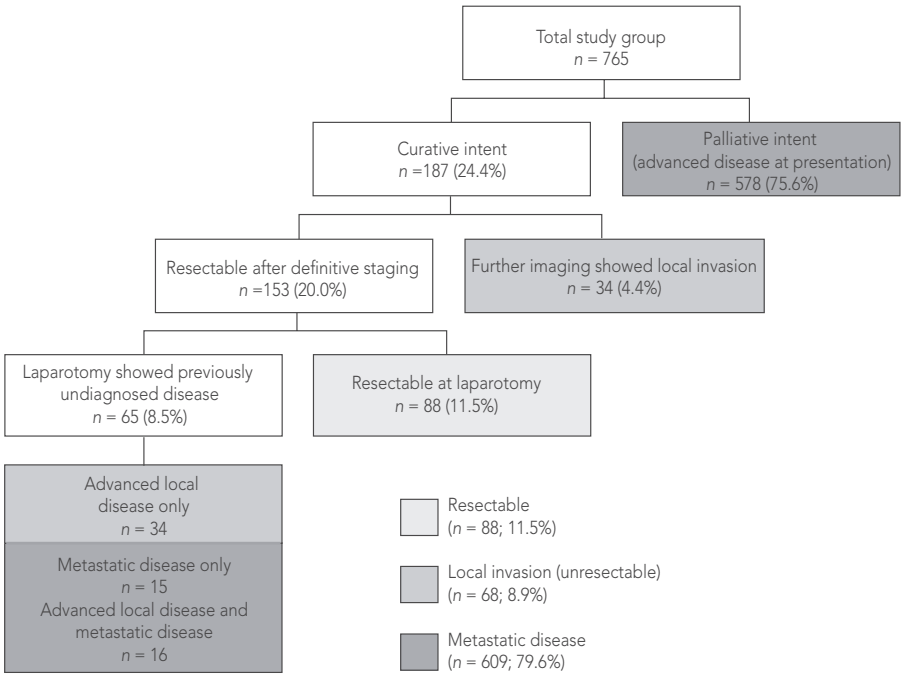
RESULTS

Patients

Of 1044 patients identified from the VCR, 927 were eligible for the study. Reasons for ineligibility included incomplete diagnostic information or notification by death certificate only. Completed surveys were obtained for 831 of the 927 eligible patients, a response rate of 89.6%. Patients with tumours of the ampulla of Vater and neuroendocrine tumours were excluded from the analysis, leaving 765 patients. Only 52 patients (6.8%) were managed in a multimodality clinic. Box 1 shows patients by treatment intent and disease stage.

Chemotherapy was considered for 413 patients (54.0%); 66 of these patients were not offered chemotherapy — mostly because of rapid disease progression, poor

1 Treatment intent and surgical resectability for patients diagnosed with pancreatic cancer during 2002–2003 in Victoria



performance status or medical comorbidities (25, 17 and 16 patients, respectively) — and 45 declined chemotherapy. Completed questionnaires were obtained for 275 of the 302 patients who received chemotherapy (response rate, 91.1%).

Radiotherapy was considered for 162 patients; 15 of these patients were advised against radiotherapy — because of no clear indication for treatment, poor performance status or comorbidities, or advanced stage disease (two, five and eight patients, respectively) — and 13 declined radiotherapy. Completed questionnaires were obtained for 119 of the remaining 134 eligible patients (response rate, 88.8%).

Chemotherapy

Of the patients who received chemotherapy and for whom questionnaires were completed (275/765; 35.9% of the study cohort), the main referral sources were specialist hepatopancreaticobiliary (HPB) surgeons (97/275; 35.3%), general surgeons (52/275; 18.9%), general practitioners (50/275; 18.2%) or gastroenterologists (32/275; 11.6%). Patients were frequently referred to other specialists, particularly palliative care physicians (74/275; 26.9%), radiation oncologists (56/275; 20.4%) and gastroenterologists (18/275; 6.5%). Ongoing follow-up was provided primarily by medical oncologists (208/275; 75.6%) and GPs (60/275; 21.8%). Forty-two patients (15.3%) were treated with chemotherapy as part of various clinical trials, most of which were treatment studies.

Chemotherapy was most commonly used for patients with advanced cancer as palliative treatment (185/275; 67.3%). Forty-five patients (16.4%) received chemotherapy in combination with radiation therapy as radical treatment, 41 (14.9%) received postoperative adjuvant chemotherapy, and four (1.5%) received neoadjuvant treatment.

Chemotherapy as palliative treatment. Among the patients treated with chemotherapy as a palliative treatment, single-agent gemcitabine was the most common treatment (154/185; 83.2%). The age of patients who received palliative chemotherapy broadly reflected the age of patients with pancreatic cancer:[1] 33.5% were 70 years or older (62/185), and 7.6% were 80 years or older (14/185). Duration of treatment varied from 1 day to more than 24 weeks, with 29.2% of patients (54/185) receiving chemotherapy for 6–12 weeks, 28.1% (52/185) for 12–24 weeks and 10.8% (20/185) for more than 24 weeks (unknown duration for 2.7%, 5/185). Treatment was discontinued owing to the planned course being complete (21/185; 11.4%), disease progression (109/185; 58.9%), poor tolerance (24/185; 13.0%), patient choice (11/185; 5.9%), deteriorating general health (10/185; 5.4%), and unspecified reasons (10/185; 5.4%). Median overall survival for patients treated with single-agent gemcitabine was 6.6 months (Box 2).

Chemoradiation as radical treatment. Patients who received radical chemoradiation represented 24.0% (45/187) of those treated with curative intent. Chemotherapy most commonly comprised infusional 5-fluorouracil (22 patients), gemcitabine alone (nine patients), or gemcitabine in combination with other agents (nine patients) (most commonly capecitabine or infusional 5-fluorouracil [four and three patients, respectively]). Thirty-one patients completed all planned treatments. A response assessment was completed for 33 patients; a complete response (no evidence of disease) was reported for three patients, a partial response (significant disease shrinkage) was reported for nine, 12 had stable disease, and nine had evidence of progressive disease. Of the 27 patients for whom information on symptoms was available, symptoms improved in 12 patients, did not change in two and worsened in nine, and four patients remained asymptomatic. Median overall survival for patients who received radical chemoradiation was 13.1 months.

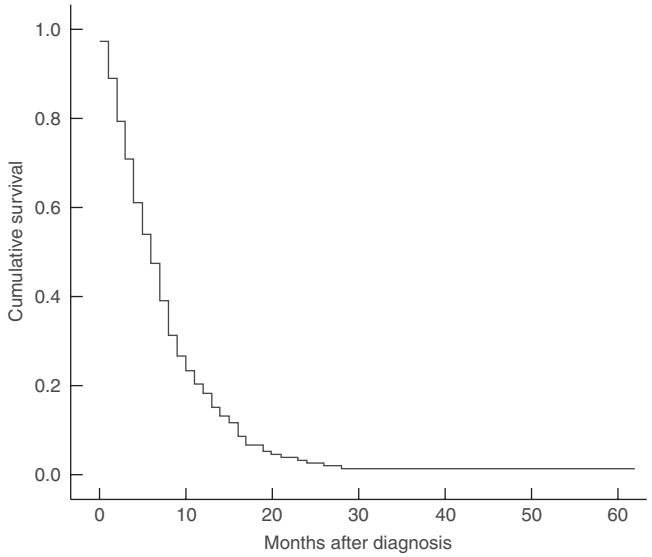
Chemotherapy as postoperative adjuvant treatment. Of the 41 patients who received postoperative adjuvant chemotherapy, 21 received 5-fluorouracil — alone by infusion, by bolus injection with leucovorin or in combination with oxaliplatin (17, three and one patient, respectively). Nineteen patients received gemcitabine — alone, with infusional 5-fluorouracil or with carboplatin (13, five and one patient, respectively). One patient received epirubicin, cisplatin and 5-fluorouracil. Treatment duration was generally between 4 and 24 weeks. Twenty-five patients completed all planned treatment; treatment was discontinued for six patients due to poor tolerance and discontinued for nine patients due to disease progression.

Chemotherapy as neoadjuvant treatment. Four patients received neoadjuvant chemotherapy — three received gemcitabine and one received infusional 5-fluorouracil. Disease progression was reported for one of these patients, and a partial response was reported for two.

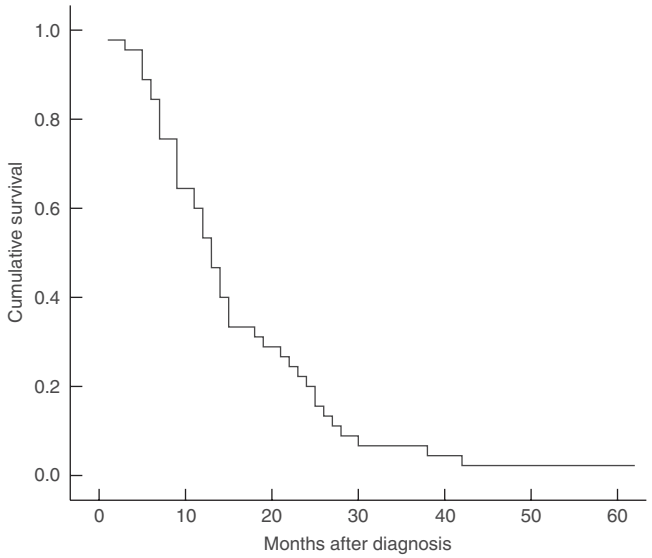
Radiotherapy

Of the patients who received radiotherapy and for whom questionnaires were com-

2 Survival of 154 patients with advanced pancreatic cancer who were treated with single-agent gemcitabine with palliative intent (median overall survival, 6.6 months)



3 Survival of 45 patients with locally advanced pancreatic cancer who were treated with chemoradiation with curative intent (median overall survival, 13.1 months)



pleted (119/765; 15.6% of the study cohort), referrals were mostly from medical oncologists (95; 79.8%), general surgeons (9; 7.6%) and HPB surgeons (5; 4.2%). According to Eastern Cooperative Oncology Group (ECOG) performance status (a scale measuring fitness and wellbeing, where 0 is fully active and able to carry on all pre-disease performance without restriction and 4 is completely disabled and confined to bed or chair), patients who received radiotherapy generally had a reasonable performance status: a score of 0 for 6.7% of patients (8/119), 1 for 35.3% of patients (42/119) and 2 for 15.1% of patients (18/119). The score was unknown for 45 patients (37.8%), 3 for five patients and 4 for one patient. Ten patients who received radiotherapy (8.4%) were treated as part of a clinical trial.

Twenty-six of 119 patients (21.8%) were referred for postoperative adjuvant radiotherapy (alone or in combination with chemotherapy), 45 (37.8%) were referred for potentially curative, radical treatment of locally advanced disease, and 46 (38.7%) had palliative treatment for advanced disease. The other two patients had pre-operative combined chemoradiation.

Radiotherapy as postoperative adjuvant treatment. Of the 26 patients who were referred for postoperative radiotherapy, the most common reasons for referral were involved or close surgical margins (22 patients) and involved locoregional lymph nodes (12 patients). Twenty referrals were from a medical oncologist, rather than a surgeon. All patients received concurrent chemotherapy — mostly infusional 5-fluorouracil. Twenty-five patients underwent three-dimensional computer planning and were treated with at least three fields. The most commonly used dose-fractionation schedule was 50.4 gray (Gy) in 28 fractions (15 patients), and 24 patients received a radiation dose of at least 45 Gy. Treatment was generally well tolerated, with only eight of the 26 patients requiring treatment for toxicity — mostly grade 1–2 (mild–moderate) nausea. Median overall survival for patients who received postoperative radiotherapy was 16.0 months.

Chemoradiation as radical treatment. Of the 45 patients referred for curative, radical radiotherapy 41 were referred by a medical oncologist. All received concurrent chemotherapy. Nine patients were enrolled in a clinical trial, some of whom received concurrent gemcitabine. Most patients (43/45) underwent three-dimensional computer planning. Patients were generally treated with a three-field or four-field technique (23 and 21 patients, respectively). Forty-three patients were treated with a dose of at least 45 Gy; 25 patients received 50.4 Gy in 28 fractions and 12 received 54 Gy in 30 fractions. Chemoradiation-related toxicity requiring treatment occurred in 13 patients, consisting mainly of nausea and vomiting (11 patients), and seven patients required a break in treatment. Median overall survival for patients who received radical chemoradiation was 13.1 months (Box 3).

Radiotherapy as palliative treatment. Of the 46 patients who were referred for palliative radiotherapy, 33 were referred by a medical oncologist, five by a general surgeon, and two by a gastroenterologist. Palliative radiotherapy was delivered to both the primary tumour and to sites of symptomatic metastatic disease, most commonly bone metastases. Three-dimensional computer planning was used for 38 patients, and 13 received concurrent chemotherapy. In contrast to radical radiotherapy, 50% of patients (23/46) were treated with either a single-field or two-field technique. The most commonly used dose-fractionation schedule was 30 Gy in 10 fractions (14 patients). Palliative radiotherapy was well tolerated, with only nine patients requiring treatment for toxicity — mainly nausea and vomiting (eight patients).

Follow-up after radiotherapy. Radiation oncologists provided follow-up after radiotherapy for only four patients. Follow-up was provided by a variety of clinicians, alone or in combination, with the most common being medical oncologists (101 patients), GPs (12) or palliative care doctors (10).

DISCUSSION

This study described the use of chemotherapy and radiation treatment in people diagnosed with pancreatic cancer in Victoria during 2002–2003. In this cohort, chemotherapy and radiotherapy were underused, few patients were managed in a multimodality clinic, and outcomes for patients were generally poor, though consistent with results from published trials. A key strength of the study was the high response rate.

To our knowledge, this study is one of few population-based surveys of the management of pancreatic cancer. Clinical management surveys can help promote informed patient choices and may result in development and implementation of standard protocols, identification and reduction of variations in practice, promotion of multidisciplinary care and clinical research, and collection and reporting of standard datasets.[17]

We found low rates of use of chemotherapy and radiotherapy in patients with pancreatic cancer. Consistent with other studies, including an evaluation of the United States National Cancer Data Base of 100 000 people with pancreatic cancer, a large proportion of people did not have any cancer-directed treatment.[6,18] Although some patients were considered too unwell for cancer-directed treatment, for many there were no clear reasons why they were not referred for consideration of such treatment.

Low referral rates to medical and radiation oncologists may be related to general pessimism regarding the impact of these treatments for people with pancreatic cancer. We have previously shown that gastroenterologists and general surgeons appear to be more pessimistic than HPB surgeons and medical and radiation oncologists.[19] Consistent with this finding, medical oncologists were the most common referral source for consideration of radiotherapy in our study. Also, in patients who were referred for postoperative radiotherapy, most referrals (20/26) were by a medical oncologist, rather than a surgeon.

Optimal use of chemotherapy and radiotherapy might be improved if all cases of pancreatic cancer were managed in a multidisciplinary setting and discussed in a multidisciplinary team meeting. In this study, a very small proportion of patients were managed in a multimodality clinic. It has been suggested that the increased use of multimodality therapy over time has been associated with a beneficial impact on survival.[5] Currently, in Victoria, there is a government-led push for greater use of multidisciplinary care teams, as well as documentation of discussions from multidisciplinary team meetings, including reportable key indicators.

All patients without obvious metastatic disease should be assessed by a specialist HPB surgeon to consider potential resectability. However, the optimal management of patients with locally advanced, unresectable pancreatic cancer is controversial. Options include radical chemoradiation, chemotherapy alone, stenting for obstructive symptoms and best supportive care.

Concerns about the potential toxicity of abdominal irradiation may contribute to low referral rates for radical chemoradiation. These concerns have arisen primarily from results of older studies that used outdated radiotherapy techniques. With current techniques of radiotherapy planning and delivery, it is possible to more accurately target tumours, while minimising dose delivered to surrounding normal tissue. In our study, most patients who received radiotherapy underwent modern three-dimensional computer planning and were treated using multiple-field conformal techniques. Chemoradiation was generally well tolerated — 13 of 45 patients required treatment for toxicity, mainly nausea and vomiting.

Trials comparing chemoradiation to chemotherapy alone for patients with locally advanced pancreatic cancer have produced conflicting results. Several early small trials suggested a significantly longer survival following chemoradiation compared with chemotherapy or radiotherapy alone.[7-9] A recently reported study, in which 119 patients with locally advanced pancreatic cancer were randomly assigned to receive gemcitabine chemotherapy alone or chemoradiation, showed superior overall survival for patients who received gemcitabine chemotherapy alone (median survival, 13.0 months v 8.6 months; $P = 0.03$). One-year survival was 53% and 32%, respectively, which led to early closure of the trial.[20] Recently reported results from an ECOG trial (E4201), in which 74 patients with locally unresectable pancreatic cancer were randomly assigned to receive gemcitabine alone or chemoradiation followed by further gemcitabine, showed that patients in the chemoradiation arm had a higher median survival than patients who received gemcitabine alone (11.0 v 9.2 months; $P = 0.04$).[21]

Radical chemoradiation should be considered for patients with locally advanced pancreatic cancer who have good performance status. Patients in this study who received radical chemoradiation had a median overall survival of 13.1 months, consistent with other published findings.[7-9] In contrast, results from the primary questionnaire in this study (not yet published) showed that patients undergoing stent insertion or bypass surgery had median overall survival of 3–6 months.

The benefit of postoperative adjuvant therapy was subject to debate in 2002 and 2003 — when the patients in our study were diagnosed — and has remained controversial.[10-15] In 1985, it was suggested that median survival was improved with postoperative adjuvant chemoradiation and maintenance 5-fluorouracil chemotherapy, compared with no postoperative adjuvant therapy.[13] Another study suggested that postoperative adjuvant therapy provides a survival advantage for patients with carcinoma of the pancreatic head.[22] A key trial, reported in 2004, has added to the controversy: the European Study Group for Pancreatic Cancer 1 Trial showed that adjuvant chemotherapy resulted in a significant survival benefit, whereas adjuvant chemoradiotherapy had a deleterious effect on survival.[12] This study has been heavily criticised, primarily because of concerns about surgical and radiation therapy quality control and randomisation methodology.

Most patients with pancreatic cancer have metastatic disease at presentation; these patients may gain symptomatic benefit and a small survival advantage from systemic chemotherapy.[16] Treatment is generally well tolerated. The pivotal trial of gemcitabine chemotherapy for patients with advanced, unresectable pancreatic cancer showed that 23.8% of patients gained clinical benefit defined as a sustained (> 4 week) improvement in at least one of pain, performance status and weight, without worsening of the others.[16] Median overall survival was 5.7 months. Similarly, we showed that gemcitabine chemotherapy, used as a palliative treatment, was well tolerated and associated with a median overall survival of 6.6 months.

In conclusion, our findings suggest that chemotherapy and radiotherapy were underused in patients with pancreatic cancer in Victoria during 2002–2003. Although the reasons for underuse are unclear, it does not appear that patients declined treatments that they were made aware of. However, patients who were treated with radical chemoradiation or palliative chemotherapy gained clinical benefits consistent with clini-

cal trial data. Management of patients in a multidisciplinary setting might lead to optimal use of chemotherapy and radiotherapy, and development and implementation of treatment guidelines could lead to better patient outcomes.

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COMPETING INTERESTS

None identified.

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