Pancreatic cancer: surgical management and outcomes after 6 years of follow-up

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Abstract

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

Design, setting and patients: Retrospective study based on questionnaires completed from medical histories of patients diagnosed with pancreatic cancer during 2002–2003 in Victoria who were identified from the Victorian Cancer Registry and followed up for 6 years.

Main outcome measures: Proportion of patients receiving each form of treatment, 30-day mortality, median survival, and 5-year and 6-year survival.

Results: Of 1044 patients with pancreatic cancer identified, 927 were eligible for the study, and questionnaires were completed for 830 (response rate, 89.5%); 67 patients with ampulla of Vater and neuroendocrine tumours were excluded. Of the 763 remaining patients (median age, 72 years), notification of death was available for 747 (97.9%). Most patients (n = 548) had tumours in the head and neck of the pancreas. Resection was performed in a total of 87 patients (11.4%). Patients managed with Whipple resection (n = 75) had a 30-day mortality rate of 5.3% and median survival of 16.3 months. A relatively large number of surgeons (n = 31) each performed a modest number of Whipple resections during the study period. Jaundice was palliated with biliary stents (n = 240) and bypass surgery (n = 99). Survival was shortest in those treated with best supportive care (median, 2.3 months for those with head and neck of pancreas tumours, and 3.4 months for body and tail of pancreas tumours). Of the 20 patients who survived to 5 years, 10 did not have histological confirmation of carcinoma and were presumably false-positive diagnoses, and three of the 10 patients who did have positive histological results had experienced recurrent disease by 6-year follow-up.

Conclusions: Most outcomes in Victoria compared favourably with other studies. Prognosis for patients with carcinoma of the pancreas is grim, with few long-term survivors. Six-year survival appears to be a better proxy for cure than 5-year survival.

Pancreatic cancer is the fourth leading cause of cancer-related mortality in Australia.[1] Median survival from diagnosis is about 5 months. The 5-year survival rate is less than 5%, but higher rates (between 6.8% and 17%) have been reported in those selected for surgery.[2-4] Patients with unresectable disease have short survival times but benefit from palliative treatment.[5,6] Results of resection and treatment in trials or published case series may not be achieved in clinical practice, as many patients are older and have more extensive disease than those included in randomised trials or referred to tertiary centres.

The Victorian Cooperative Oncology Group, in collaboration with the Victorian Cancer Registry (VCR), examined patterns of care for patients diagnosed with pancreatic cancer over a 2-year period. Here, we describe the surgical management of and outcomes for these patients. Chemotherapy and radiotherapy in this cohort have been described previously.[7]

Methods

We conducted a survey of all Victorian residents diagnosed with pancreatic carcinoma during 2002 or 2003 who were identified by the VCR. Ethics approval was obtained from the Cancer Council Victoria Human Research Ethics Committee.

Treating doctors were sent a questionnaire relating to treatment intent, management and outcomes. Data collection commenced in 2005. All patients were followed up for 6 years through mortality data from the Victorian Registry of Births, Deaths and Marriages and the National Death Index.

Statistical analysis

Overall survival was estimated using Kaplan–Meier methods, and mean and median survival are presented with standard errors (SEs). The log-rank test was used to compare survival between groups. Mortality was assessed according to surgeon caseload. Surgeons were ranked according to number of laparotomies performed for attempted Whipple resection. Most results are presented as percentages, with χ^2 statistics used to compare groups.

Results

A total of 1044 patients with a diagnosis of pancreatic cancer in 2002 or 2003 were identified. Of these, 117 (11.2%) were deemed ineligible because the diagnosis was found to have occurred outside the study interval, the patient was not a usual resident of Victoria, or no treatment information was available because the notification to the VCR was by death certificate or autopsy only.

Completed questionnaires were received for 830 of the 927 eligible patients (response rate, 89.5%). For the remaining 97 patients, the patient record was unavailable (16), doctors declined to participate or did not respond (57), or there was insufficient information to include the patient in the survey (24). Patients with neuroendocrine tumours or tumours of the ampulla of Vater (67) were also excluded, leaving 763 patients with cancer of the pancreas in the study sample.

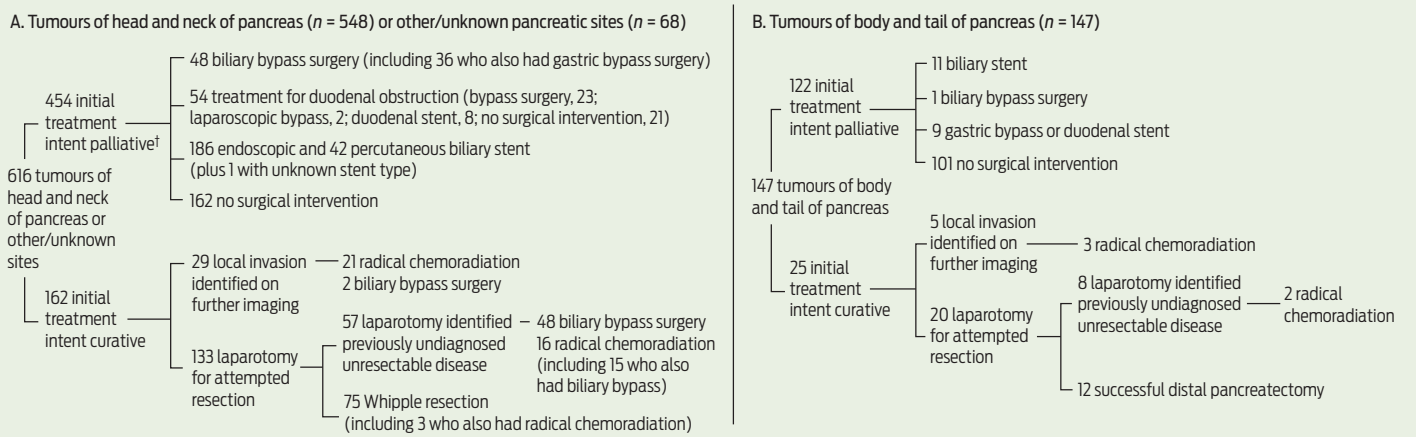
The median age of the included patients was 72 years, and 391 (51.2%) were male. Only 44 patients (5.8%) were younger than 50 years, and 196 (25.7%) were aged 80 years or older.

Surgical management

Surgical management of patients is shown in Box 1. Resection was performed in a total of 87 patients (11.4%).

Of the 616 patients with a tumour in the head and neck of the pancreas, or other or unspecified pancreatic sites, the initial treatment intent was palliative for 454 (73.7%) and curative

1 Surgical management of patients with pancreatic cancer,* by site of tumour



* Patients not ultimately accounted for in the flow charts did not have any of the specified treatment options.
† Patients may have received more than one type of treatment. ◆

2 Survival and 30-day mortality by tumour site, procedure and chemotherapy

Procedure	No. of patients*	Median age†	30-day mortality‡	Survival (months)§
Head and neck of pancreas and other or unknown sites				
All	616	73	95 (15.4%)	4.5 (0.3)
Whipple resection	75	68	4 (5.3%)	16.3 (2.7)
Radical chemoradiation	40	67	0	13.1 (1.1)
Biliary bypass	98	69	7 (7.0%)	6.5 (0.7)
Referred for Whipple resection	50	65	2 (3.8%)	9.4 (1.0)
Palliative intent	48	73	5 (10.4%)	3.9 (0.9)
Biliary stent for palliative treatment¶				
Endoscopic	186	77	24 (12.9%)	3.7 (0.5)
Percutaneous	42	76	6 (14.3%)	2.8 (0.5)
Gemcitabine treatment	46	67	0	6.5 (1.9)
No gemcitabine	183	79	30 (16%)	3.2 (0.3)
Treatment for duodenal obstruction	54	72	4 (7.0%)	5.3 (1.1)
No surgical intervention**	162	76	49 (30.2%)	2.3 (0.3)
Gemcitabine treatment	31	62	0	5.6 (1.0)
No gemcitabine	131	77	49 (37%)	1
Body and tail of pancreas				
All	147	71	31 (21.1%)	3.9 (0.4)
Distal pancreatectomy	12	67	0	12.7 (16.8)
Biliary stent for palliative treatment	11	69	0	5.6 (0.7)
Treatment for duodenal obstruction	9	65	2 (28.6%)	5.6 (2.2)
No surgical intervention**††	101	72	29 (24.6%)	3.4 (0.5)
Gemcitabine treatment	25	65	4 (16%)	6.5 (0.9)
No gemcitabine	74	74	23 (31%)	2.4 (0.4)

* Groups are not mutually exclusive (ie, a patient may appear in more than category). For example, the biliary bypass group contains 15 patients who also had radical chemoradiation. † At diagnosis. ‡ Number of deaths within 30 days of diagnosis date (% of people having this procedure). § Median (standard error). ¶ One stent did not have type identified. ** No resection, bypass or stenting. †† Gemcitabine treatment status unknown for two patients. ◆

for 162 (26.3%). Whipple resection (pancreaticoduodenectomy) was performed in 75 patients (12.2%).

Of the 147 patients with a tumour in the body and tail of the pancreas, 122 (83.0%) were managed with palliative intent, and 25 (17.0%) with curative intent. Distal pancreatectomy was performed in 12 patients (8.2%).

Bypass surgery

A total of 99 patients, comprising two broad groups, had biliary bypass surgery (Box 1). In one group of 48 patients, unresectable disease was found during laparotomy for attempted resection, and bypass surgery was performed instead. Another two patients had bypass surgery after unresectable local invasion was shown on further imaging before laparotomy. In the other group of 49 patients, imaging identified more extensive disease, with metastases or local invasion, and bypass surgery was planned as an initial palliative procedure.

Of these 99 patients, 33 had cholecystojejunostomy and 53 had choledochojejunostomy. The type of biliary bypass was not specified for 13 patients. Gastrojejunostomy was performed in addition to biliary bypass for duodenal compression or prophylactically in 23 patients.

Biliary stents

Biliary stents were the initial palliative treatment in 240 patients (Box 1) and were used to treat biliary obstruction occurring after initial treatment in 15 patients (13 after bypass surgery, two after Whipple resection). Biliary stents were used for preoperative drainage in 86 of 162 patients referred for Whipple resection.

Most stents (274/327; 83.8%) were placed endoscopically, while 50 (15.3%) were placed percutaneously, usually after a failed endoscopic attempt (in 30 patients). Jaundice recurred in 69 patients and was managed with repeat endoscopic stenting.

All preoperatively placed endoscopic stents were plastic. Both plastic (102) and metal (67) endoscopic stents were used for initial palliation (type was unknown in 71 patients).

Survival and mortality

Median survival and 30-day mortality for each treatment group are shown in Box 2.

Patients managed with Whipple resection had a median survival of 16.3 months (mean, 25 months); four patients (5.3%) died within 30 days, and seven (9.3%) within 90 days. Median survival of patients with positive margins was 13.9 months, compared with 20.6 months for those with clear margins (Box 3).

Patients with tumours in the body and tail of the pancreas managed with distal pancreatectomy had a median survival of 8.3 (SE, 3.1) months for those with positive margins ($n = 3$) and 36.6 (SE, 14.3) months for those with clear margins ($n = 9$).

The surgeon's identity was known for 98 of 133 laparotomies performed for attempted Whipple resection. In the 2-year study period, three surgeons performed nine or more laparotomies (32 patients), seven surgeons performed four to eight (35 patients), and 21 surgeons performed less than four (31 patients). The 30-day mortality (3.2%, 5.5% and 3.1%, respectively; $P = 0.84$) and the mean crude survival (15.7 [SE, 2.9], 19.3 [SE, 3.3] and 15.8 [SE, 2.8] months, respectively) were similar for each group of surgeons.

Compared with patients who had bypass surgery for initial palliation in unresectable disease, those having bypass surgery after being referred for Whipple resection had lower 30-day mortality (3.8% v 10.4%; $P < 0.001$), and better median survival (9.4 v 3.9 months; $P < 0.001$) (Box 2).

Patients who were managed conservatively with no surgical intervention had short survival and high 30-day mortality (Box 2).

Patient selection

The proportions of patients in each age group receiving various treatments are shown in Box 4. Compared with older groups, greater proportions of patients in younger groups underwent Whipple resection, chemoradiation, and gemcitabine treatment. Similar proportions of patients in the youngest and oldest age groups were managed with biliary stents and conservative treatment.

Long-term survivors

Date-of-death notifications were available for 747 patients (97.9%). Sixteen patients (2.1%) were confirmed to be alive after 6 years of follow-up.

Twenty patients (2.6%) survived for at least 5 years after diagnosis. Of these, 10 had been treated with resection, three with biliary stenting but no resection, three with no intervention, one with bypass surgery, one with chemoradiotherapy, one with stenting plus chemotherapy, and one with chemotherapy alone. Histological results were positive for carcinoma in all patients treated with resection, but none of those managed without resection had a biopsy confirming carcinoma.

Six-year follow-up of the 10 patients who survived to 5 years after resection found that two had died from recurrent disease and one from other causes, one was alive with recurrent metastatic disease, and six were alive with no evidence of recurrence. Nine of the 10 managed without resection remained alive at 6 years, with the other one having died from causes unrelated to cancer.

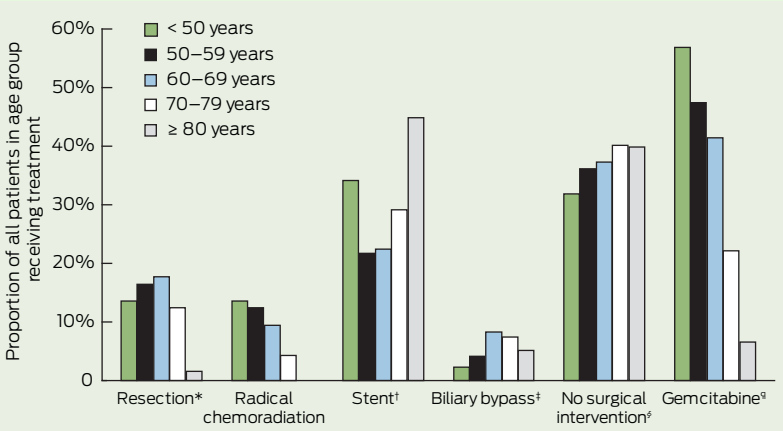
The 5-year and 6-year survivals for patients referred for consideration of resection, patients having a laparotomy for attempted resection, and patients with completed resection are shown in Box 3.

3 Survival of patients with carcinoma of head and neck of the pancreas, by subgroups reflecting progressively less extensive disease

Patient group	30-day mortality	Median survival (SE), months	5-year survival	6-year survival
Carcinoma of head and neck of pancreas or other/unspecified site ($n = 616$)	15.4%	4.5 (0.3)	2.6%	0.3%
Referred for Whipple resection ($n = 162$)	3.1%	12.2 (0.7)	5.6%	1.2%
Laparotomy for Whipple resection ($n = 133$)	3.8%	12.6 (1.1)	6.0%	1.5%
Whipple resection ($n = 75$)	5.3%	16.3 (2.7)	8.0%	2.7%
Margins involved ($n = 29$)	6.9%	13.9 (0.9)	0	0
Clear margins ($n = 44$)	4.5%	20.6 (4.1)	13.6%	4.5%
Number of those who had resection surviving			10	7

SE = standard error. ◆

4 Proportions of patients in each age group receiving each treatment, for all tumour types



* Includes both Whipple resection and distal pancreatectomy. † Head and neck of pancreas tumours — stent for initial palliation. ‡ Head and neck of pancreas tumours — biliary bypass for initial palliation. § No resection, stent or biliary bypass. ¶ With or without any other treatment. ◆

Discussion

The findings of this study represent an unbiased population-based picture of the surgical management and outcomes of patients diagnosed with carcinoma of the pancreas in 2002 and 2003 in Victoria. Strengths of the study include a response rate of almost 90%, together with high case ascertainment by the VCR due to mandatory cancer reporting, and the

near complete follow-up of survival through mortality data. A limitation is the retrospective collection of data.

The management of carcinoma of the pancreas is often benchmarked on the results of surgical resection. Resection rates should be greater than 10% in unselected patients, and early mortality, observed median survival and 5-year survival are important end points.[8,9] In this study, Whipple resection was performed in 12% of all patients presenting with tumours of the head and neck of the pancreas, comparable to reported rates of 10%–15%.[9,10] Thirty-day mortality in these patients (5.3%) was comparable to reports from individual hospitals.[9] A large epidemiological study in the United States reported 30-day mortality of 7.5%, and a survey of 23 hospitals in England and Wales reported 12%.[11,12] Although inhospital or 90-day mortality are better measures of perioperative mortality, they are not as widely reported. Median survival in the patients undergoing Whipple resection in this study (16.3 months) is comparable with other reports, and their 5-year survival of 8% is comparable to results from a review of eight similar series (range, 3.7%–16.4%).[9,13]

We found that a relatively large number of surgeons each performed a modest number of Whipple resections during the 2-year study period, but early mortality and survival were not related to surgeon workload. However, investigations in larger populations have found that early mortality rate and survival improve with increasing workloads for both surgeons and hospitals.[11] The US National Comprehensive Cancer Network guidelines recommend pancreatic resection be done at hospitals that perform more than 20 resections annually.[14] Chang and colleagues report excellent results from a high-volume centre in New South Wales and suggest most Whipple resections should be performed in high-volume specialist units.[15] Implementation of this strategy has been difficult in other countries,[16] and others argue that volume-based referrals undermine local expertise and may leave patients' care far from supportive social networks, and therefore suggest that only high-risk patients be referred to high-volume centres.[11]

The proportion of patients in this study with positive resection margins (38.7%) was higher than in most other reports (14%–40%).[17] Identification of involved resection margins depends on both the definition being used and the individual pathologist. In experienced hands, the rate of positive resection margins should be about 20%.[18] As the rate of positive margins decreases with increasing workload,[17] the higher rate in our study may be related to the low annual workload of most of the surgeons.

Twenty patients in our study (2.6%) survived at least 5 years. However, half of these patients were managed palliatively without histological confirmation of carcinoma and presumably represent false-positive diagnoses. A review of 23 3-year survivors found only 11 had histological confirmation of carcinoma, and cautioned that including patients without histological confirmation would falsely inflate the survival rate.[19] Therefore, the actual 5-year survival in our study is best recorded as 10 patients (1.3%). A previous report of outcomes in Victoria found a more optimistic 5-year survival rate of 5%.[2] The difference may be explained by lack of detailed clinical follow-up in that study, resulting in the inclusion of false-positive diagnoses reported to the VCR.

Unfortunately, 5-year survival does not equal cure. We found that disease recurred after 5 years in three of 10 patients treated with resection. During long-term follow-up after Whipple resection, one study found recurrent carcinoma in five of 12 patients between 5 and 6 years of follow-up, and another reported that four of 11 5-year survivors later died of recurrent disease.[13,20] These findings suggest that 6-year survival is a better proxy for cure than 5-year survival.

Older age, more advanced disease, and poor performance status are significant predictors of poor survival.[21-23] Comparisons of outcomes from different management strategies should be adjusted for the patient characteristics in each group. The influence of patient selection can be seen in the outcomes of bypass surgery in this study. Bypass patients who had been referred for Whipple resection but found to have unresectable disease at laparotomy were younger and had better outcomes than those referred initially for palliative surgery.

Guidelines recommend that biliary obstruction in frail elderly patients with limited life expectancy is best palliated with endoscopic stenting.[8] Compared with bypass surgery, endoscopic stenting has been found to have lower early mortality and morbidity, although recurrent jaundice is more common due to stent blockages.[24] In our study, bypass surgery was used as initial palliation for unresectable tumours in similar proportions of younger and older patient groups, including 6.6% of patients aged 80 years or older. The selection of elderly patients for bypass surgery may be due to patient preference for local management in regional hospitals or to difficulty accessing endoscopic stenting.

Chemotherapy with gemcitabine reduces symptoms, with a modest improvement in survival, and should be offered to all patients with advanced disease and good performance status.[25] In this study, gemcitabine was used more often in younger patients with a good performance status, as judged by 30-day mortality. Other studies have found that a decreasing proportion of patients receive chemotherapy with advancing age.[21] Our results have been reported in detail previously.[7]

An important question when discussing major surgery is: What is the chance of cure? A survey of oncologists and their patients in NSW found that 98% of patients would like realistic information about their prognosis.[26] The rate of 5-year survival after Whipple resection is often quoted as about 20%.[14,15] However, this outcome refers to those with a clear resection margin — a subgroup that can only be identified after surgery. The outcomes for all those undergoing a laparotomy for Whipple resection are more relevant for informing the process of consent before surgery. We found that these patients have a 5-year survival of 6%, but the 6-year survival (1.5%) is a more realistic estimate of the probability of cure. On the other hand, patients with tumours in the head or

neck of the pancreas managed with best supportive care had median survival of only 2.3 months — much less than the overall median survival of 4.5 months — and benefit from early referral to palliative care.

The population-based nature of this study avoids the biases inherent in descriptions of outcomes from a single institution. We found that outcomes for carcinoma of the pancreas in Victoria in 2002–2003 were comparable to those reported in other multicentre studies and from single institutions. Carcinoma of the pancreas has a grim prognosis, with few long-term survivors. We found that half of the long-term survivors among patients reported to the VCR had false-positive diagnoses, and previous estimates of long-term survival may therefore have been optimistic. Disease recurrence in 5-year survivors is common, and 6-year survival is a better proxy for cure.

Competing interests: No relevant disclosures.

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1 Thursfield V, Farrugia H, Robertson P, Giles G, editors. Canstat No. 49: Cancer in Victoria 2008. Melbourne: The Cancer Council Victoria, 2010. http://www1.petermac.org/allg/NewSite/NewsEvents/canstatsVIC_08.pdf (accessed Feb 2012).

2 English D, Farrugia H, Thursfield V, et al. Cancer survival Victoria 2007. Estimates of survival in 2004 (and comparisons with earlier periods). Melbourne: The Cancer Council Victoria, 2007. http://www.cancervic.org.au/downloads/cec/survival-2007/Cancer-Survival-2007.pdf (accessed Feb 2012).

3 Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? *Ann Surg* 1995; 221: 59-66.

4 Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; 4: 567-579.

5 Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the US: utilization, outcomes, and the effect of hospital volume. *Cancer* 2007; 110: 1227-1234.

6 Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database. *J Am Coll Surg* 1999; 189: 1-7.

7 Jefford M, Thursfield V, Torn-Broers Y, et al. Use of chemotherapy and radiotherapy in patients with pancreatic cancer in Victoria (2002–2003): a retrospective cohort study. *Med J Aust* 2010; 192: 323-327.

8 Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, Royal College of Pathologists, Special Interest Group for Gastro-Intestinal Radiology. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut* 2005; 54 Suppl 5: v1-v16.

9 Beger HG, Rau B, Gansauge F, et al. Treatment of pancreatic cancer: challenge of the facts. *World J Surg* 2003; 27: 1075-1084.

10 Niederhuber JE, Brennan MF, Menck HR. The National Cancer Data Base report on pancreatic cancer. *Cancer* 1995; 76: 1671-1677.

11 Teh SH, Diggs BS, Deveney CW, Sheppard BC. Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines. *Arch Surg* 2009; 144: 713-721.

12 Bachmann MO, Alderson D, Peters TJ, et al. Influence of specialization on the management and outcome of patients with pancreatic cancer. *Br J Surg* 2003; 90: 171-177.

13 Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. *Ann Surg* 1996; 223: 273-279.

14 Tempero MA, Arnoletti JP, Behrman S, et al; NCCN Pancreatic Adenocarcinoma. National Comprehensive Cancer Network Clinical Practice Guidelines for Oncology. Pancreatic Adenocarcinoma. *J Natl Compr Canc Netw* 2010; 8: 972-1017. http://www.jnccn.org/content/8/9/972.long (accessed Feb 2012).

15 Chang DK, Merret ND, Biankin AV; NSW Pancreatic Cancer Network. Improving outcomes for operable pancreatic cancer: is access to safer surgery the problem? *J Gastroenterol Hepatol* 2008; 23: 1036-1045.

16 van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg* 2005; 242: 781-788.

17 Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. *J Am Coll Surg* 2008; 207: 510-519.

18 Adams RB, Allen PJ. Surgical treatment of resectable and borderline resectable pancreatic cancer: expert consensus statement by Evans et al [comment]. *Ann Surg Oncol* 2009; 16: 1745-1750.

19 Connolly MM, Dawson PJ, Michelassi F, et al. Survival in 1001 patients with carcinoma of the pancreas. *Ann Surg* 1987; 206: 366-373.

20 Trede M, Schwall G, Saeger HD. Survival after pancreaticoduodenectomy. 118 consecutive resections without an operative mortality. *Ann Surg* 1990; 211: 447-458.

21 Krzyzanowska MK, Weeks JC, Earle CC. Treatment of locally advanced pancreatic cancer in the real world: population-based practices and effectiveness. *J Clin Oncol* 2003; 21: 3409-3414.

22 Shaib YH, Davila JA, El-Serag HB. The epidemiology of pancreatic cancer in the United States: changes below the surface. *Aliment Pharmacol Ther* 2006; 24: 87-94.

23 Katz MH, Hwang R, Fleming JB, Evans DB. Tumour-node-metastasis staging of pancreatic adenocarcinoma. *CA Cancer J Clin* 2008; 58: 111-125.

24 Smith AC, Dowsett JF, Russell RC, et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. *Lancet* 1994; 344: 1655-1660.

25 Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403-2413.

26 Hagerty RC, Butow PN, Ellis PM, et al. Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis. *J Clin Oncol* 2005; 23: 1278-1288. ❑