Published in final edited form as:

Ann Surg Oncol. 2010 February ; 17(2): 371–376. doi:10.1245/s10434-009-0759-z.

Impact of Selection Bias on the Utilization of Adjuvant Therapy for Pancreas Adenocarcinoma

Andrew J. Russ, MD¹, Sharon M. Weber, MD¹, Robert J. Rettammel, MA¹, David M. Mahvi, MD^{1,2}, Layton F. Rikkers, MD¹, and Clifford S. Cho, MD¹

Clifford S. Cho: cho@surgey.wisc.edu

¹Section of Surgical Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI

²Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL

Abstract

Background—Improved outcomes have been associated with the use of adjuvant therapy after resection of pancreas adenocarcinoma. However, the frequency with which patients receive adjuvant therapy and the factors impacting its use remain largely undefined. We hypothesized that nonutilization of adjuvant therapy was primarily associated with patient comorbidity and onset of postoperative complications.

Methods—A prospectively maintained database was reviewed to identify patients who underwent potentially curative resection of histologically confirmed pancreas adenocarcinoma at our institution from January 1996 to May 2007. Clinicopathological data and postoperative treatment history were collected to identify variables associated with receipt of adjuvant therapy.

Results—Of 119 patients, 33% did not receive adjuvant therapy. The frequency with which patients underwent adjuvant therapy did not change over time. On multivariate analysis, patient age 70 years or greater, major postoperative complications, distal pancreatectomy, absence of nodal metastases, and absence of perineural invasion were associated with decreased utilization of adjuvant therapy.

Discussion—One-third of patients in this contemporary dataset of patients did not go on to receive adjuvant therapy. The likelihood of receiving adjuvant treatment is negatively impacted by the course of postoperative recovery. Moreover, the fact that adjuvant therapy was undertaken less often for older patients and patients with favorable pathological features highlights the selection bias impacting the decision to pursue postoperative therapy for this disease. This selective utilization of postoperative therapy for patients with adverse oncological characteristics is likely to bias any retrospective analysis attempting to measure the efficacy of adjuvant treatment for pancreas adenocarcinoma.

Outcomes for patients diagnosed with pancreas adenocarcinoma remain poor, with an annual case-to-fatality ratio of approximately 0.91.^{1,2} For patients presenting with localized resectable tumors, 5-year survival estimates following resection remain 10–30%.^{2–6} Recent

retrospective series and randomized controlled trials suggest a demonstrable improvement in outcomes associated with administration of adjuvant therapy.^{3,6–10} Indeed, the contemporary management of patients with resectable pancreas adenocarcinoma takes advantage of a multidisciplinary approach that includes surgical resection and systemic gemcitabine-based chemotherapy with or without radiation therapy. In reality, not all patients undergoing surgical resection of pancreas adenocarcinoma receive adjuvant therapy. However, the likelihood with which patients go on to receive postoperative adjuvant therapy and the factors influencing that likelihood remain largely undefined. We evaluated our own institutional experience to determine how often patients undergo adjuvant therapy after resection of pancreas adenocarcinoma, and to identify the clinicopathological variables that negatively impact the ability of patients to receive adjuvant treatment. We hypothesized that patient age and postoperative complications were the primary determinants of whether patients went on to receive adjuvant oncological therapy following surgical resection.

Methods

After obtaining institutional review board approval, a prospectively maintained single-institution database was retrospectively reviewed to identify patients who underwent potentially curative (R0 or R1) resection of pancreas adenocarcinoma at the University of Wisconsin Hospital and Clinics between 1996 and May 2007. Patients treated with neoadjuvant therapy, patients with incomplete medical records, and patients found on repeat histological review to have non-pancreas-adenocarcinoma diagnoses (e.g., ampullary adenocarcinoma, distal cholangiocarcinoma) or nonadenocarcinoma diagnoses (e.g., noninvasive premalignant lesions, neuroendocrine neoplasms) were excluded from our analysis. Patient characteristics [age, gender, preoperative serum CA 19-9 level, type of operation (pancreaticoduodenectomy or distal pancreatectomy), and year of operation], pathological characteristics (tumor size, histological grade, perineural invasion, resection margin status, and nodal metastases), and postoperative characteristics (length of hospital stay, development of complications, complication grade, and initiation of adjuvant chemotherapy or chemotherapy and radiation) were collected. For purposes of statistical analysis, operation timing was categorized into one of three time periods (1996–1999, 2000–2003, 2004–2007). Complications were graded using a previously defined five-point classification system: grade 1 complications required oral medications or bedside care; grade 2 complications required intravenous medications; grade 3 complications required operative or radiological interventions; grade 4 complications resulted in chronic disability or unintended organ resection; grade 5 complications resulted in death.¹¹ Complications of grade 3 or above were considered major complications. Clinical, pathological, and postoperative characteristics associated with likelihood of adjuvant chemotherapy were identified using chi-square univariate analysis. Variables with p values ≤ 0.1 on univariate analysis were examined by multivariate analysis using the binary logistic regression model. Statistical significance was defined as $p < 0.05$.

Results

We identified 142 patients who underwent surgical resection of histologically confirmed pancreas adenocarcinoma at our institution between 1996 and May 2007. Four patients who

underwent R2 resection and 13 patients who received neoadjuvant therapy were excluded. Six patients were excluded due to incomplete follow-up; therefore, 119 patients meeting all inclusion criteria comprised the dataset for this analysis. Patient, pathological, and postoperative characteristics are outlined in Table 1. Gender was evenly distributed, and median age was 69 years. The majority of patients underwent pancreaticoduodenectomy, and more patients underwent operation in later years when the dataset was divided into 4-year time periods (1996–1999, 2000–2003, 2004–2007). Median tumor size was 3 cm, and microscopic margin positivity, nodal metastases, and perineural invasion, were observed in 32%, 57%, and 42%, respectively. Median length of postoperative hospitalization was 9 days, and 14% developed at least one major (grade 3 or above) complication in the postoperative period. The observed 60-day mortality rate was 1.7%. One-third of patients undergoing surgical resection did not receive adjuvant therapy. Of the 80 patients who received adjuvant therapy, 29 (36%) received chemotherapy alone and 51 (64%) received chemotherapy and radiation.

As outlined in Table 2, patient age greater or equal to 70 years, performance of distal pancreatectomy, smaller tumor size (pT1 or pT2), absence of nodal metastases, negative resection margin, absence of perineural invasion, prolonged length of postoperative stay, and onset of major postoperative complications were associated with decreased likelihood of receiving adjuvant therapy on univariate analysis. The frequency with which patients underwent adjuvant therapy did not appear to change over time.

As shown in Table 3, age greater than or equal to 70 years, distal pancreatectomy, absence of nodal metastases, absence of perineural invasion, and major complication remained independently associated with decreased likelihood of receiving adjuvant therapy on multivariate analysis.

Discussion

Several retrospective studies have observed a survival benefit associated with use of adjuvant chemotherapy after resection of pancreas adenocarcinoma.^{6,8,12} These observations have been substantiated by a number of randomized controlled trials. The Gastrointestinal Study Group (GITSG) trial reported improved estimated 5-year survival for patients receiving adjuvant 5-fluorouracil compared with patients treated with surgical resection alone (18% vs. 0%).^{7,13} Similarly, the European Study Group for Pancreatic Cancer (ESPAC-1) trial observed an estimated 5-year survival of 21% among patients receiving adjuvant 5-fluorouracil versus 8% among patients who did not.³ The Charité Onkologie (CONKO-001) trial comparing the use of adjuvant gemcitabine versus observation alone identified an improvement in estimated 5-year disease-free survival associated with the use of adjuvant gemcitabine (16.5% vs. 5.5%).⁹ A recent meta-analysis of randomized clinical trials examining the efficacy of adjuvant therapy identified a 25% reduction in the risk of death associated with the use of adjuvant chemotherapy that reached statistical significance.¹⁴

In the present analysis, we evaluated our own institutional experience with patients undergoing potentially curative resection of pancreas adenocarcinoma to identify the frequency with which these patients go on to receive adjuvant therapy, and to identify the

variables associated with the likelihood of not receiving adjuvant therapy. We observed that 33% of our patients did not initiate adjuvant therapy in the postoperative period. This figure is not dissimilar to the experience collected in retrospective and prospective analyses from other institutions. In a single-institution prospective analysis that identified a survival benefit associated with the use of adjuvant chemoradiation, 31% of patients offered adjuvant therapy declined to receive postoperative treatment.¹⁵ Similarly, Sohn and colleagues published a 27% incidence of failure to go on to receive postoperative therapy.¹² In the ESPAC-1 and CONKO-001 randomized controlled trials, 50% and 38% of patients, respectively, assigned to receive adjuvant chemotherapy either did not start or prematurely discontinued postoperative therapy.^{3,9}

The variables we found to be associated with decreased administration of postoperative therapy were advanced patient age, prolonged postoperative hospitalization, postoperative complications, early T stage, pN0 status, absence of perineural invasion, R0 status, and distal pancreatectomy. Despite our relatively small dataset, we elected to utilize multivariate analysis because of the potential of multicollinearity between some of these factors. The variables that retained independent significance (advanced age, postoperative complications, absence of nodal metastases or perineural invasion, and distal pancreatectomy) reinforced the suggestion that the delivery of adjuvant treatment is undermined by patient comorbidity, suboptimal postoperative recovery, favorable oncological features, and performance of distal pancreatectomy.

We hypothesized that failure to initiate adjuvant chemotherapy would be primarily referable to preoperative patient comorbidities and the development of postoperative complications. Indeed, both advanced age (a potential marker of preexisting comorbidity) and the onset of major (grade 3 and above) postoperative complications were both independently associated with lower likelihood of receiving adjuvant therapy. As summarized in Fig. 1, 76% of patients younger than 70 years of age received adjuvant therapy, in contrast to only 58% of patients aged 70 years or older ($p = 0.038$). Of patients who experienced no postoperative complications, 77% went on to receive adjuvant therapy; this was statistically indistinguishable from the 72% of patients who experienced minor (defined as grade 1 or 2) complications receiving adjuvant therapy. In stark contrast, only 31% of patients developing major (grade 3 or above) complications ultimately received adjuvant treatment ($p = 0.003$). Previous analyses have implicated postoperative complications and delayed postoperative recovery as factors impeding the delivery of adjuvant chemotherapy.^{16,17} In contrast, Aloia et al. observed that failure to receive adjuvant therapy was driven not by delayed postoperative recovery but by lower preoperative performance scores and urgent operations.¹⁸ Importantly, patient age and postoperative complications remained independently associated with decreased likelihood of receiving adjuvant therapy on multivariate analysis, suggesting that some physicians may favor avoidance of adjuvant chemotherapy with or without radiation and their attendant risks for elderly patients.

The impact of this likely selection bias is also illustrated by the association between various favorable oncological variables and nonutilization of adjuvant treatment. On univariate analysis, negative resection margins, absence of nodal metastases, and absence of perineural invasion were each associated with lower likelihood of initiating adjuvant treatment. On

multivariate analysis, absence of nodal metastases and absence of perineural invasion remained independently associated with lower likelihood of initiating adjuvant therapy. The survival benefit associated with the use of adjuvant therapy has not been definitively stratified by oncological features such as tumor stage.¹⁹ As a result, prospectively acquired data informing the decision of which patients may (or may not) benefit from adjuvant therapy do not exist. A likely explanation for our observed relationships is clinical selection bias: the potential risk of adjuvant chemotherapy with or without radiation may be felt to outweigh its marginal benefit for some patients with “favorable” oncological findings. Clearly, our collective appreciation for the oncological benefit of adjuvant therapy has been informed by the growing number of clinical trials published in recent years demonstrating its efficacy. Interestingly, we observed that the relationships between oncological variables and receipt of adjuvant therapy remained unchanged between the three time periods we examined (1997–1999, 2000–2003, and 2004–2007) (Fig. 1).

The explanation for the impact of the type of pancreatectomy performed on adjuvant therapy is less clear. Although adenocarcinoma in the body or tail of the pancreas is generally less likely to be resectable at presentation, patients with resectable left-sided tumors have similar postresection survival to patients with resectable tumors in the pancreatic head, and relatively favorable outcomes have been described for patients undergoing adjuvant therapy after resection of left-sided pancreatic adenocarcinoma.^{20–22} It is conceivable that a perception of left pancreatectomy as being less radical than pancreaticoduodenectomy may impart a selection bias affecting the decision to recommend additional oncological therapy.

This selection bias may have implications for nonrandomized analyses examining the impact of adjuvant therapy. If postoperative therapy is preferentially administered to patients with adverse oncological characteristics, the therapeutic benefit of adjuvant therapy may be muted. A plurality of retrospective analyses have found some benefit to adjuvant therapy for patients with resected pancreas adenocarcinoma; it is therefore possible that the benefit of adjuvant chemotherapy may actually be more substantial than these data have demonstrated.

This study is clearly limited by the retrospective nature of its analysis. It was not possible to reliably identify the reasons for not pursuing adjuvant therapy for patients who received no postoperative oncological treatment. Because of the tertiary referral nature of our medical center, many patients were advised to pursue adjuvant therapy postoperatively but did not do so after returning to their local care providers. We also were unable to reliably determine whether patients who went on to initiate adjuvant therapy were able to complete their prescribed regimens. It is also possible that incorporation of adjuvant therapy in our institution may differ from those occurring in nontertiary referral centers. A recent analysis of practice patterns across the USA identified utilization rates of only 5.7% and 38.7% for adjuvant chemotherapy and adjuvant chemoradiation, respectively, after resection of pancreas adenocarcinoma during the time period encompassed by our study.²³ Thus, the potential selection biases we have highlighted may not be reflective of practice patterns elsewhere. Importantly, the influence of selection bias in this clinical circumstance should not be unexpected, nor is it necessarily inappropriate. The decision to recommend any oncological therapy is a heavily nuanced one that is informed by an understanding of treatment risk and oncological benefit; indeed, the relatively marginal benefit that can be

ascribed to adjuvant therapy for resected pancreas adenocarcinoma makes it difficult to universally impose its incorporation into algorithms and guidelines for all patients. Nevertheless, it is important to recognize the impact of this bias in the allocation of adjuvant treatment strategies for this challenging disease. Our observations suggest that any retrospective analysis of the efficacy of adjuvant therapy is likely to be confounded by the unequal distribution of patients who do and do not receive adjuvant therapy after surgical resection; proper recognition of this bias will be needed to best evaluate our current management of this difficult disease.

References

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005; 55(2): 74–108. [PubMed: 15761078]
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin.* 2006; 56(2):106–30. [PubMed: 16514137]
3. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004; 350(12):1200–10. [PubMed: 15028824]
4. Keedy VL, Berlin J. Adjuvant and neoadjuvant approaches to treat surgically resectable pancreatic cancer. *Curr Treat Options Oncol.* 2006; 7(5):381–8. [PubMed: 16904055]
5. Sener SF, Fremgen A, Menck HR, et al. 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):1–7. [PubMed: 10401733]
6. Katz MH, Wang H, Fleming JB, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. *Ann Surg Oncol.* 2009; 16(4):836–47. [PubMed: 19194760]
7. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. *Cancer.* 1987; 59(12):2006–10. [PubMed: 3567862]
8. Murakami Y, Uemura K, Sudo T, et al. Postoperative adjuvant chemotherapy improves survival after surgical resection for pancreatic carcinoma. *J Gastrointest Surg.* 2008; 12(3):534–41. [PubMed: 18026816]
9. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA.* 2007; 297(3):267–77. [PubMed: 17227978]
10. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA.* 2008; 299(9):1019–26. [PubMed: 18319412]
11. Martin RC II, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. *Ann Surg.* 2002; 235(6):803–13. [PubMed: 12035036]
12. 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(6):567–79. [PubMed: 11307091]
13. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg.* 1985; 120(8):899–903. [PubMed: 4015380]
14. Butturini G, Stocken DD, Wenthe MN, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. *Arch Surg.* 2008; 143(1):75–83. [PubMed: 18209156]
15. Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. *Ann Surg.* 1997; 225(5):621–33. [PubMed: 9193189]

16. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol.* 1997; 15(3):928–37. [PubMed: 9060530]
17. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg.* 1999; 230(6):776–82. [PubMed: 10615932]
18. Aloia TA, Lee JE, Vauthey JN, et al. Delayed recovery after pancreaticoduodenectomy: a major factor impairing the delivery of adjuvant therapy? *J Am Coll Surg.* 2007; 204(3):347–55. [PubMed: 17324767]
19. Merchant NB, Rymer J, Koehler EAS, et al. Adjuvant chemoradiation therapy for pancreatic adenocarcinoma: who really benefits? *J Am Coll Surg.* 2009; 208(5):829–41. [PubMed: 19476845]
20. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. *Ann Surg.* 1996; 223(5):506–11. [PubMed: 8651741]
21. Ozaki H, Kinoshita T, Kosuge T, et al. An aggressive therapeutic approach to carcinoma of the body and tail of the pancreas. *Cancer.* 1996; 77(11):2240–5. [PubMed: 8635090]
22. Murakami Y, Uemura K, Sudo T, et al. Impact of adjuvant gemcitabine plus S-1 chemotherapy after surgical resection for adenocarcinoma of the body or tail of the pancreas. *J Gastrointest Surg.* 2009; 13(1):85–92. [PubMed: 18704593]
23. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S.: utilization, outcomes, and hospital volume. *Cancer.* 2007; 110(6):1227–34. [PubMed: 17654662]

Fig. 1.

Table 1
Patient, pathological, and postoperative characteristics

Variable	n (%)
Gender	
Female	57 (48%)
Male	62 (52%)
Age at operation (years)	
Median (range)	69 (35–88)
Operation	
Pancreaticoduodenectomy	103 (87%)
Left pancreatectomy	16 (13%)
Time period of operation	
1996–1999	29 (24%)
2000–2003	38 (32%)
2004–2007	52 (43%)
Preoperative CA19-9 (U/mL)	
Median (range)	208 (0–12,101)
Tumor size (cm)	
Median (range)	3 (0.4–10)
pT stage	
Median (range)	3 (1–4)
pT1	11 (9%)
pT2	35 (30%)
pT3	64 (54%)
pT4	8 (7%)
Histological grade	
Low	27 (26%)
Intermediate	63 (60%)
High	15 (14%)
Resection margin	
Positive	38 (32%)
Negative	81 (68%)
Nodal metastases	
Positive	68 (57%)
Negative	51 (43%)
Perineural invasion	
Positive	50 (42%)
Negative	69 (58%)
Length of postoperative hospitalization	
Median, days (range)	9 (4–41)
<7 days	19 (16%)
7–13 days	81 (68%)

Variable	n (%)
14–20 days	11 (9%)
21 days	8 (7%)
Complication grade	
None/minor (grade 0–2)	106 (89%)
Major (grade 3)	13 (11%)
Adjuvant therapy	
No	39 (33%)
Yes	80 (67%)
Type of adjuvant therapy	
Chemotherapy alone	29 (36%)
Chemotherapy plus radiation	51 (64%)

CA19-9 serum carbohydrate antigen 19-9

Table 2

Univariate analysis

Variable	No adjuvant	Adjuvant	<i>p</i>
Gender			
Female	18 (32%)	39 (68%)	0.472
Male	21 (34%)	41 (66%)	
Age at operation			
<70 years	15 (24%)	47 (76%)	0.038
70 years	24 (42%)	33 (58%)	
Operation			
Pancreaticoduodenectomy	29 (28%)	74 (72%)	0.006
Left pancreatectomy	10 (62%)	6 (38%)	
Time period of operation			
1996–1999	12 (41%)	17 (59%)	0.506
2000–2003	12 (32%)	26 (68%)	
2004–2007	15 (29%)	37 (71%)	
Preoperative CA19-9			
<200 U/L	10 (26%)	29 (74%)	0.449
200 U/L	14 (33%)	28 (67%)	
Tumor size			
<3 cm	19 (35%)	35 (65%)	0.603
3 cm	19 (31%)	43 (69%)	
pT3 or more			
No	21 (46%)	25 (54%)	0.020
Yes	18 (25%)	54 (75%)	
Histological grade			
Low	9 (33%)	18 (67%)	0.192
Intermediate	15 (24%)	48 (76%)	
High	7 (47%)	8 (53%)	
Resection margin			
Negative	32 (40%)	49 (60%)	0.022
Positive	7 (18%)	31 (82%)	
Nodal metastases			
Negative	23 (45%)	28 (55%)	0.013
Positive	16 (24%)	52 (76%)	
Perineural invasion			
Negative	30 (43%)	39 (57%)	0.003
Positive	9 (18%)	41 (82%)	
Length of postoperative hospitalization			
<21 days	33 (30%)	78 (70%)	0.008
21 days	6 (75%)	2 (25%)	
Complication grade			

Variable	No adjuvant	Adjuvant	<i>p</i>
None/minor (0–2)	30 (28%)	76 (72%)	
Major (3)	9 (69%)	4 (31%)	0.003

Statistically significant variables are indicated in bold

CA19-9 serum carbohydrate antigen 19-9

Table 3
Multivariate analysis

Variable	<i>p</i>	OR
Age 70 years	0.003	(5.053)
Left pancreatectomy	0.018	(5.525)
Negative resection margin	0.970	
pT1 or pT2	0.168	
Absence of nodal metastases	0.011	(3.817)
Absence of perineural invasion	0.001	(6.667)
Length of postoperative hospitalization 21 days	0.419	
Major complication (grade 3)	0.008	(10.219)

Statistically significant variables are indicated in bold

OR odds ratio