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Failure of Normalization of CA19-9 Following Resection for Pancreatic Cancer is Tantamount to Metastatic Disease

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Abstract

Background—Multidisciplinary therapy for pancreatic cancer involves radical resection followed by gemcitabine-based chemotherapy. Carbohydrate antigen 19-9 (CA19-9), when elevated preoperatively, is a useful marker to monitor disease status following resection. However, little has been reported on outcomes of patients in whom CA19-9 never normalizes. We hypothesize that failure of CA19-9 normalization within 6 months is prognostically equivalent to metastatic disease.

Methods—From our pancreatectomy database, we identified 93 patients with pancreatic adenocarcinoma and elevated CA19-9 prior to resection with levels recorded postoperatively. Patients were grouped based on normalization or persistent elevation of CA19-9 at 6 months after resection. CA19-9 levels normalized (≤ 35 u/ml) after resection in 38 (41%) and remained elevated in 55 (59%). Clinicopathologic characteristics were compared using Student's *t*-test and contingency table analyses. Survival curves were constructed using Kaplan–Meier method and compared by log-rank analysis. Cox regression was used to determine predictors of survival.

Results—The two groups had comparable clinicopathologic characteristics except for nodal status and perineural invasion, which were higher in patients with persistently elevated CA19-9. Persistent CA19-9 conferred shorter median overall survival of 10.8 months compared with 23.8 months in patients with normalization ($p < 0.001$), which persisted when controlling for nodal status. Multivariate analysis demonstrated persistently elevated CA19-9 as the sole statistically significant negative predictor of survival [hazard ratio (HR) 2.20, $p = 0.002$].

Conclusions—Persistent CA19-9 elevation after pancreatectomy correlates with shorter survival analogous to unresected or metastatic disease and should be regarded as persistent disease regardless of radiographic findings. These patients should be considered for accrual to clinical trials or initiation of alternative therapy.

Pancreas cancer remains one of the most lethal cancers. In the USA, there were an estimated 42,470 newly diagnosed cases in 2009. Of continued concern are the estimated 35,240

deaths from pancreas cancer in 2009, being the fourth leading cause of cancer death among both genders.¹ This dismal prognosis owes to the propensity for early metastasis and, hence, late presentation as well as its inherent resistance to conventional chemotherapy and radiation. As such, surgical resection remains the only hope for cure, with adjuvant chemotherapy offering modest improvement in survival.² Current National Comprehensive Cancer Network (NCCN) guideline recommendations support use of 5-fluorouracil (5-FU)-based chemoradiation with additional gemcitabine chemotherapy or single-agent chemotherapy alone with gemcitabine (preferred chemotherapy), capecitabine, or 5-FU after pancreatectomy followed by observation.³ However, it is difficult to determine who benefits most from adjuvant chemotherapy given the high recurrence rates.

There have been multiple serum- and tissue-based markers that have been investigated as potential prognostic tools in pancreatic cancer.^{4,5} Carbohydrate antigen 19-9 (CA19-9) is well recognized as an important marker for diagnosis and prognosis in pancreatic cancer.⁶⁻⁸ In advanced disease, rise and fall in CA19-9 levels act as surrogates of progressive disease and response to therapy, respectively, in clinical trials in spite of lack of changes in radiographic tumor burden.⁹ However, patients without radiographically detectable disease after curative resection who have persistently elevated CA19-9 levels are generally not eligible for clinical trials testing novel therapies or second-line therapy designed for those with metastatic disease. While most clinicians agree that patients who fail to have normalization of CA19-9 levels after curative resection for pancreatic cancer have undetected metastatic disease, little has been reported regarding outcomes in these patients following surgery. As such, we sought to determine survival following curative resection in patients with pancreatic cancer and the impact of postoperative CA19-9 changes relative to tumor stage.

PATIENTS AND METHODS

Patients

This study protocol was approved by the Institutional Review Board at The Ohio State University. Between 1998 and 2008, 317 patients who underwent pancreatectomy for pancreatic cancer were identified from our database. This group was then examined to identify patients with preoperative and postoperative CA19-9 level measurements. From this, we were able to identify 93 patients with elevated CA19-9 levels prior to resection and CA19-9 levels measured after pancreatectomy. We elected to use a 6-month cutoff for time to normalization of CA19-9 levels to allow an adequate period of time for postoperative recovery, resolution of biliary and/or pancreatic duct obstruction, completion of adjuvant therapy when administered, and time for acquisition and normalization of CA19-9 levels prior to disease recurrence.¹⁰

Patients were stratified into two groups based on the postoperative CA19-9 nadir: those with normalization (≤ 35 u/ml) of CA19-9 levels within 6 months of resection and those with persistent elevation of CA19-9 levels 6 months after resection. Postoperative CA19-9 levels within 6 months normalized after resection in 38 (41%) patients and remained persistently elevated in 55 (59%).

Preoperative workup for patients analyzed included radiologic staging, biochemical labs, and routine medical assessment. Regarding radiologic staging, helical computerized tomography (CT) of abdomen/pelvis (pancreas protocol) was routinely obtained. Chest imaging included either chest X-ray (CXR) or chest CT to rule out evidence of thoracic metastatic disease. Given this, it is theoretically possible that patients who underwent CXR preoperatively could have undetected thoracic metastatic disease. However, isolated thoracic disease without abdominal metastases is uncommon, and patients with extrapancreatic

abdominal disease would not have gone on to resection and been included in this patient cohort.

As postoperative surveillance was not protocol driven, radiographic assessment was not standardized. In accordance with standard accepted practice, patients routinely underwent restaging cross-sectional imaging after they recovered from their surgery and/or prior to initiation of adjuvant therapy to assess for evidence of recurrence or metastatic disease.

Statistical Analysis

Patients' demographics and clinicopathologic characteristics were compared between groups using Student's *t*-test for continuous variables and contingency table analysis (chi-square or Fisher exact test, where appropriate) for categorical variables. Statistical test results were two sided, and $p < 0.05$ was considered statistically significant.

Demographic analysis for comorbidities was undertaken incorporating the Charlson comorbidity index, an index that assesses patient risk based on major comorbid conditions.¹¹ Major comorbidities included heart disease (coronary artery disease, congestive heart failure), pulmonary disease, kidney disease, cerebrovascular disease, liver disease, diabetes mellitus with/without end organ damage, connective tissue disease, ulcer disease, and history of other cancers.

Survival Analysis

Survival data were obtained on all patients through the use of our institution's electronic/paper medical record and the Social Security Death Index (SSDI; <http://ssdi.rootsweb.ancestry.com>) as of 28 January 2010 (last SSDI update) to determine date of patient's expiration. Length of survival was determined from the date of surgery to date of expiration from any cause or to the date of most recent SSDI update (28 January 2010) in living patients. Statistical survival analysis was undertaken using the Kaplan-Meier method with group comparisons by log-rank analysis. Multivariate analysis was undertaken using Cox proportional-hazards regression using a forward selection, likelihood ratio (LR) model. Two perioperative deaths were excluded from all survival analyses. All statistical analyses were completed using SPSS 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Demographic/Clinicopathologic Analysis

There were no significant demographic differences between patients with and without normalization of their postoperative CA19-9 levels in terms of age, gender, associated major comorbidities, and adjuvant therapy administration (Table 1). Postoperatively, 78/93 (84%) patients had followup data regarding adjuvant treatment. While adjuvant therapy was offered to all of these patients, 62/78 (79%) received adjuvant therapy and the remaining 16 (21%) did not. This difference was not statistically significant ($p = 0.08$). In general, those patients receiving adjuvant therapy underwent standard gemcitabine-based chemotherapy or chemoradiation therapy with 5-FU followed by gemcitabine. Those patients who demonstrated recurrence or progression were considered for second-line therapy or clinical trials.

There were no statistically significant differences between groups with regard to the clinicopathologic characteristics of mean preoperative bilirubin, preoperative biliary stenting, tumor size, tumor location, T stage, resection margin status, lymphovascular invasion, perioperative complications, perioperative mortality, median preoperative CA19-9, and postoperative nadir CA19-9 levels (Table 1). However, patients who did not have

normalization of their CA19-9 after surgery were more likely to have nodal metastases and perineural invasion. Of the 60 total patients with node(+) disease, only 17 (28.3%) had normalization of their CA19-9 after resection, whereas 21 of the 33 (63.6%) with node(−) disease had normalization of their CA19-9 levels ($p = 0.001$). Similarly, patients with perineural invasion were less likely to normalize their postoperative CA19-9. Of the 78 patients with perineural invasion, only 28 (35.9%) had normalization of their CA19-9 after resection, whereas 9 of 10 patients (90%) with absence of perineural invasion had normalization of their CA19-9 levels ($p = 0.003$). As expected, the postoperative CA19-9 nadir was higher in the persistently elevated group. These patients were also more likely to have higher CA19-9 levels prior to surgery (Table 1). On average, a greater mean percentage reduction in CA19-9 was seen per patient in the group demonstrating normalization of CA19-9 compared with patients with persistently elevated CA19-9 (85 vs. 70%, $p = 0.002$) after exclusion of 16 patients in the latter group whose CA19-9 levels increased after resection.

Survival Analysis

Overall median survival for all patients was 16.2 months. Failure to normalize CA19-9 postoperatively was associated with poorer survival (median 10.8 vs. 23.8 months, $p < 0.001$). Life table analysis demonstrated 2-year survival of 19 and 47% for persistently elevated CA19-9 and normalized CA19-9, respectively, and 3-year survival of 9 and 33% (Table 2). As expected, node-positive disease was also associated with shorter survival of 13.5 months compared with 25.2 months with node-negative disease ($p = 0.002$).

Given the impact of postoperative CA19-9 and nodal status on survival, patients were stratified into four groups: normalized CA19-9/node(−) ($n = 21$), normalized CA19-9/node(+) ($n = 17$), elevated CA19-9/node(−) ($n = 10$), and elevated CA19-9/node(+) ($n = 43$). Patients with persistently elevated postoperative CA19-9 had worse survival than those who normalized their CA19-9 regardless of lymph node status ($p = 0.001$, Fig. 2). Patients with node-negative disease who had normalization of their CA19-9 had the longest overall survival. Patients with node-positive disease who had normalization of CA19-9 still had median overall survival nearly twice that of those with node-negative disease who failed to normalize their CA19-9 (Table 3).

Univariate analyses were undertaken of all measured variables to determine those most likely to predict survival (Table 4). Persistently elevated postoperative CA19-9 ($p < 0.001$), perineural invasion ($p = 0.05$), and node-positive disease ($p = 0.002$) were the only predictors of survival on univariate analysis. However, on multivariate analysis, the only statistically significant predictor of survival was persistently elevated postoperative CA19-9 level [$p = 0.002$, HR = 2.20, 95% confidence interval (CI) 1.22–3.63] (Fig. 1, Table 4).

DISCUSSION

Overall, pancreas cancer portends very poor prognosis, even in the minority of patients who are amenable to surgical resection. Undoubtedly, dismal results after resection stem from progression of metastatic disease occult at time of surgery. Presently, clinicians generally utilize surgical pathologic characteristics, radiographic surveillance, and CA19-9 levels to guide treatment strategies. Our investigation and analysis suggest a potentially important role of postoperative CA19-9 levels to direct therapy and certainly to predict outcome.

We limited our investigation to patients in our pancreatic cancer database who underwent radical resection with curative intent, had elevated preoperative CA19-9, and had CA19-9 followed in the early postoperative period. The resultant 93 patients were then divided into two groups based upon normalization of CA19-9 at 6 months. We chose this 6-month cutoff

to allow adequate time for recovery from surgery, relief of biliary or pancreatic obstruction, and completion of all or the majority of any adjuvant therapy yet prior to the time where elevations in CA19-9 could be accounted for by appearance of recurrent disease. Using these criteria, we found the two groups to be similar in nearly all clinicopathologic characteristics measured with the exception of presence of nodal metastases and perineural invasion. This is certainly not unexpected given the association of these factors with more biologically aggressive disease. However, when we controlled for these variables, failure of CA19-9 to normalize remained the sole predictor of poorer survival, increasing the risk of death by a factor greater than two.

Our survival outcomes are similar to those of a study published by Safi et al. that also examined the prognostic significance of CA19-9 in patients with persistently elevated levels versus patients with normalized levels, demonstrating survival of 10.9 and 32.2 months ($p = 0.0001$), respectively.¹² An interesting finding of our subgroup analysis was the difference in survival seen when patients were stratified into four groups accounting for both postoperative CA19-9 trend and nodal status. Arguably, the CA19-9 response after surgery is a more powerful predictor of survival than nodal status given the increased survival in patients with node-positive disease who normalized their CA19-9 compared with those without nodal metastases who did not meet this same endpoint (Table 3, Fig. 2).

This study has several potential limitations to acknowledge. This study was undertaken in a retrospective fashion from a database of patients spanning 1998–2008. Though there have not been major advances in diagnosis and treatment of pancreatic cancer, this study design lends to the introduction of potential biases. Any small improvements that have been seen with the use of gemcitabine-based chemotherapy, radiation therapy, and more aggressive surgical approaches incorporating vascular reconstructions and radical lymphadenectomy may have led to better outcomes, albeit slight, in patients treated more recently. Additionally, in this study design, there were a large number of patients who were excluded due to inadequate acquisition and followup of CA19-9 levels. Immeasurable factors may influence when and why CA19-9 levels were obtained, thus potentially influencing the ultimate outcomes. Still, using common clinicopathologic characteristics, no differences were seen between groups.

Multiple studies have examined the implications and significance of elevated preoperative CA19-9 levels and their correlation to outcomes.^{13–16} There have been limited studies regarding the implications of postoperative CA19-9 levels that suggest that elevated and rising postoperative CA19-9 levels confer reduced survival.^{12,17–19} We propose that failure of normalization of CA19-9 may be of major prognostic significance and, despite a lack of efficacious treatments, should play a role in guiding alternative therapy. We suggest that all patients with suspected pancreatic cancer should have CA19-9 levels obtained at diagnosis, as well as postoperative CA19-9 levels in those patients amenable to attempted curative resection. The postoperative CA19-9 trend may be used to aid clinicians in the appropriate course of therapy. Those patients who do not normalize their CA19-9 levels postoperatively appear to have aggressive biologic behavior similar to those with persistent or metastatic disease, with shorter survival regardless of other clinicopathologic characteristics. Hence, we advocate that accrual to clinical trials and continued or alternative therapy should be considered in these patients, even if radiographic evidence of disease is absent.

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REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin*. 2009; 59(4):225–249. [PubMed: 19474385]
2. 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):267–277. [PubMed: 17227978]
3. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™). To view the most recent and complete version of the NCCN Guidelines™, go online to NCCN.org. © 2010 National Comprehensive Cancer Network, Inc.; Pancreas Cancer (Version 1.2010). Available at: NCCN.org
4. Bloomston M, Frankel WL, Petrocca F, et al. MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis. *JAMA*. 2007; 297:1901–1908. [PubMed: 17473300]
5. Dilhoff M, Liu J, Frankel W, Croce C, Bloomston M. MicroRNA-21 is overexpressed in pancreatic cancer and a potential predictor of survival. *J Gastrointest Surg*. 2008; 12(12):2171–2176. [PubMed: 18642050]
6. Bloomston M, Bekaii-Saab TS, Kosuri K, Cowgill SM, Melvin WS, Ellison EC, Muscarella P. Preoperative carbohydrate antigen 19-9 is most predictive of malignancy in older jaundiced patients undergoing pancreatic resection. *Pancreas*. 2006; 33(3):246–249. [PubMed: 17003645]
7. Muscarella P.; Fisher, W.; Johnson, J.; Melvin, WS. Neoplastic disorders of the pancreas. In: Lott, J., editor. *Clinical pathology of pancreatic disorders*. New Jersey: Humana; 1997. p. 125-163.
8. Hernandez JM, Cowgill SM, Al-Saadi S, et al. CA19-9 velocity predicts disease-free survival and overall survival after pancreatectomy of curative intent. *J Gastrointest Surg*. 2009; 13(2):349–353. [PubMed: 18972170]
9. Bramhall SR, Rosemurgy A, Brown PD, Bowry C, Buckels JA. Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol*. 2001; 19(15):3447–3455. [PubMed: 11481349]
10. Rapellino M, Piantino P, Pecchio F, et al. Disappearance curves of tumor markers after radical surgery. *Int J Biol Markers*. 1994; 9(1):33–37. [PubMed: 8051433]
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40(5):373–383. [PubMed: 3558716]
12. Safi F, Schlosser W, Falkenreck S, Beger HG. Prognostic value of CA19-9 serum course in pancreatic cancer. *Hepatogastroenterology*. 1998; 45(19):253–259. [PubMed: 9496523]
13. Ong SL, Garcea G, Thomasset SC, et al. Surrogate markers of resectability in patients undergoing exploration of potentially resectable pancreatic adenocarcinoma. *J Gastrointest Surg*. 2008; 12(6):1068–1073. [PubMed: 18043987]
14. Fujioka S, Misawa T, Okamoto T, Gocho T, Futagawa Y, Ishida Y, et al. Preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the evaluation of curability and resectability in patients with pancreatic adenocarcinoma. *J Hepatobiliary Pancreat Surg*. 2007; 14(6):539–544. [PubMed: 18040617]
15. Ko AH, Hwang J, Venook AP, Abbruzzese JL, Bergsland EK, Temero MA. Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. *Br J Cancer*. 2005; 93(2):195–199. [PubMed: 15999098]
16. Wong D, Ko AH, Hwang J, Venook AP, Bergsland EK, Tempero MA. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. *Pancreas*. 2008; 37(3):269–274. [PubMed: 18815548]
17. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J Clin Oncol*. 2006; 24(18):2897–2902. [PubMed: 16782929]
18. Kinsella TJ, Seo Y, Willis J, et al. The impact of resection margin status and postoperative CA19-9 levels on survival and patterns of recurrence after postoperative high-dose radiotherapy with 5-FU-based concurrent chemotherapy for resectable pancreatic cancer. *Am J Clin Oncol*. 2008; 31(5):446–453. [PubMed: 18838880]

19. Berger AC, Garcia M Jr, Hoffman J, et al. Postresection CA19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol*. 2008; 26(36):5918–5922. [PubMed: 19029412]

FIG. 1. Overall survival in patients with and without normalization of postoperative CA19-9 levels after undergoing pancreatectomy with elevated preoperative CA19-9 levels

FIG. 2.
Overall survival in patients with elevated preoperative CA19-9 undergoing pancreatectomy, stratified by postoperative CA19-9 level and nodal status

TABLE 1

Demographic and clinicopathologic characteristics stratified by postoperative CA19-9 trend in patients undergoing pancreatectomy for pancreatic adenocarcinoma with elevated preoperative CA19-9

	Normalized CA19-9 (N = 38)	Persistently elevated CA19-9 (N = 55)	p-Value
Age, mean (range), years	61.7 (38–74)	65.4 (46–85)	0.10
Gender (M:F)	21:17	30:25	0.95
Major comorbidities (%)	23 (61%)	32 (58%)	0.82
Adjuvant therapy ^a	30/34 (88%)	32/44 (73%)	0.08
Tumor location (head:body/tail)	35:3	50:5	1.0
Preoperative bilirubin, mean ± SD, mg/dl	5.8 ± 6.8	4.3 ± 5.4	0.23
Preoperative CA19-9, median (range), U/mL	148.9 (36.0–7,261.3)	413.6 (35.2–26,346.2)	0.09
Postoperative CA19-9 nadir, median (range), U/mL	15.4 (1–35)	98.7 (35.3–3,612)	0.002
Preoperative biliary stent	21 (55.3%)	24 (43.6%)	0.27
Tumor size, median (range), cm	3.8 (1.0–8.0)	4.0 (1.5–11.0)	0.68
T stage			
T1	1 (2.6%)	2 (3.6%)	0.15
T2	8 (21.1%)	4 (7.1%)	
T3	29 (76.3%)	49 (89.1%)	
T4	0	0	
Node(+) disease	17 (44.7%)	43 (78.2%)	0.001
Lymphovascular invasion ^a	16/37 (43.2%)	27/51 (52.9%)	0.41
Perineural invasion ^a	28/37 (75.7%)	50/51 (98.0%)	0.003
Margin (–) status (%)	33 (86.8%)	43 (78.2%)	0.41
Perioperative complications	13 (34.2%)	22 (40.0%)	0.67
Perioperative mortality	0	2 (3.6%)	0.51

SD standard deviation

^aDenominator denotes the number of patients for whom data was documented

TABLE 2

Overall survival in patients stratified by postoperative CA19-9 levels undergoing pancreatectomy for pancreatic adenocarcinoma with elevated preoperative CA19-9

	Normalized CA19-9	Persistently elevated CA19-9	<i>p</i>-Value
Median	23.8 months	10.8 months	<0.001
1-Year	82%	45%	
2-Year	47%	19%	
3-Year	33%	9%	

TABLE 3

Overall survival comparisons stratified for postoperative CA19-9 trend and nodal status

Group	Median survival (months)	95% Confidence interval (months)	<i>p</i> -Value
Normalized CA19-9/node(−) (<i>n</i> = 21)	40.1	25.25–54.96	0.001
Normalized CA19-9/node(+) (<i>n</i> = 17)	19.8	10.52–29.08	
Elevated CA19-9/node(−) (<i>n</i> = 10)	10.9	3.46–18.34	
Elevated CA19-9/node(+) (<i>n</i> = 43)	10.3	5.80–14.80	
Overall groups	16.2	13.16–19.24	

TABLE 4

Univariate and multivariate (Cox proportional hazard regression; forward, likelihood ratio model) analyses of predictors of overall survival

Variable	Univariate	Multivariate
Age	0.22	0.08
Gender	0.79	0.47
Comorbidity	0.38	0.12
Preoperative bilirubin	0.80	0.49
Preoperative stent	0.89	0.80
Preoperative CA19-9	0.19	0.63
Tumor size	0.45	0.75
T stage	0.55	N/A ^a
Tumor location	0.60	0.66
Lymphovascular invasion	0.20	0.49
Perineural invasion	0.05	0.24
Complication	0.12	0.25
Node-positive disease	0.002	0.12
Margin-positive disease	0.35	0.12
Persistent postoperative CA19-9 elevation	<0.001	0.002 HR = 2.20 (95% CI 1.33–3.63)

Data represent *p*-values

HR hazard ratio, *CI* confidence interval, *N/A* not applicable

^aT stage excluded from multivariate analysis due to collinearity with tumor size