Advances in Radiation Oncology (2018) **3**, 154–162

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Postresection CA19-9 and margin status as predictors of recurrence after adjuvant treatment for pancreatic carcinoma: Analysis of NRG oncology RTOG trial 9704

William F. Regine MD [a,*], Kathryn Winter MS [b], Ross A. Abrams MD [c], Howard Safran MD [d], Ivan L. Kessel MD [e], Yuhchyau Chen MD, PhD [f], James A. Fugazzi MD [g], Eric D. Donnelly MD [h], Thomas A. DiPetrillo MD [d], Samir Narayan MD [i], John P. Plastaras MD [j], Rakesh Gaur MD [k], Guila Delouya MD [l], John H. Suh MD [m], Joshua E. Meyer MD [n], Michael G. Haddock MD [o], Mukund S. Didolkar MD [p], Gilbert D.A. Padula MD [q], David Johnson MD [r], John P. Hoffman MD [n], Christopher H. Crane MD [s,t]

[a] *University of Maryland School of Medicine, Baltimore, Maryland*
[b] *NRG Oncology Statistics and Data Management Center, Philadelphia, Pennsylvania*
[c] *Rush University Medical Center, Chicago, Illinois*
[d] *Rhode Island Hospital, Providence, Rhode Island*
[e] *University of Texas Medical Branch, Galveston, Texas*
[f] *University of Rochester Medical Center, Rochester, New York*
[g] *Toledo Community Hospital Oncology Program CCOP, Toledo, Ohio*
[h] *Northwestern Memorial Hospital, Chicago, Illinois*
[i] *Michigan Cancer Research Consortium CCOP, Ann Arbor, Michigan*
[j] *University of Pennsylvania Medical Center, Philadelphia, Pennsylvania*
[k] *Kansas City CCOP, Kansas City, Missouri*
[l] *Centre Hospitalier de l'Université de Montréal-Notre Dame, Montreal, Quebec*
[m] *Cleveland Clinic Foundation, Cleveland, Ohio*
[n] *Fox Chase Cancer Center, Philadelphia, Pennsylvania*
[o] *Mayo Clinic, Rochester, Minnesota*
[p] *Sinai Hospital of Baltimore, Baltimore, Maryland*

Sources of support: This project was supported by grants U10CA21661 (RTOG-Ops-Stat), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), and U10CA37422 (CCOP) from the National Cancer Institute (NCI) and Eli Lilly.

Conflicts of interest: Dr. Delouya reports personal fees from Elekta, Bayer, Astellas, and Janssen outside the submitted work. Dr. Suh reports personal fees from Varian Medical Systems and Philips as well as other fees from Elekta outside the submitted work. Ms. Winter reports the receipt of an NCI grant as a subcontract to ACR (her employer during the conduct of the study). All other authors have no conflicts of interest to declare.

* Corresponding author. Department of Radiation Oncology, University of Maryland Medical Center, 22 S. Greene Street, Room GGK-0101, Baltimore, MD 21201.

E-mail address: wregine@umm.edu (W.F. Regine).

https://doi.org/10.1016/j.adro.2018.01.003

[q] *Grand Rapids Clinical Oncology Program (GRCOP), Grand Rapids, Michigan*
[r] *St Francis Regional Medical Center, Wichita, Kansas*
[s] *The University of Texas MD Anderson Cancer Center, Houston, Texas*
[t] *Memorial Sloan Kettering Cancer Center, New York, New York*

Received 11 January 2018; accepted 16 January 2018

Abstract

Purpose: NRG Oncology RTOG 9704 was the first adjuvant trial to validate the prognostic value of postresection CA19-9 levels for survival in patients with pancreatic carcinoma. The data resulting from this study also provide information about predictors of recurrence that may be used to tailor individualized management in this disease setting. This secondary analysis assessed the prognostic value of postresection CA19-9 and surgical margin status (SMS) in predicting patterns of disease recurrence.

Methods and materials: This multicenter cooperative trial included participants who were enrolled as patients at oncology treatment sites in the United States and Canada. The study included 451 patients analyzable for SMS, of whom 385 were eligible for postresection CA19-9 analysis. Postresection CA19-9 was analyzed at cut points of 90, 180, and continuously. Patterns of disease recurrence included local/regional recurrence (LRR) and distant failure (DF). Multivariable analyses included treatment, tumor size, and nodal status. To adjust for multiple comparisons, a *P* value of ≤ .01 was considered statistically significant and > .01 to ≤ .05 to be a trend.

Results: For CA19-9, 132 (34%) patients were Lewis antigen–negative (no CA19-9 expression), 200 (52%) had levels <90, and 220 (57%) had levels <180. A total of 188 patients (42%) had negative margins, 152 (34%) positive, and 111 (25%) unknown. On univariate analysis, CA19-9 cut at 90 was associated with increases in LRR (trend) and DF. Results were similar at the 180 cut point. SMS was not associated with an increase in LRR on univariate or multivariate analyses. On multivariable analysis, CA19-9 ≥ 90 was associated with increased LRR and DF. Results were similar at the 180 cut point.

Conclusions: In this prospective evaluation, postresection CA19-9 was a significant predictor of both LRR and DF, whereas SMS was not. These findings support consideration of adjuvant radiation therapy dose intensification in patients with elevated postresection CA19-9.

Introduction

Adenocarcinoma of the pancreas remains one of the most aggressive solid tumors and the fourth most common cause of cancer death in the United States today.[1] Patients who undergo potentially curative gross total tumor resection have the best chance for cure. Although some improvements in survival have been associated with the addition of chemotherapy and/or radiation therapy (RT), survival remains limited.[2-7] Despite multiple phase 3 adjuvant trials, analyses of the correlation of surgical margin status (SMS) with pattern of disease recurrence among patients for whom postresection CA19-9 levels are also known are lacking.[2-8]

A common presumption among patients being evaluated for adjuvant therapy, and often within the conduct of multidisciplinary tumor boards, is that an elevation in postresection CA19-9 levels reflects the eminent development of distant disease spread of pancreatic cancer, without consideration of the potential risk of concurrent local/regional disease recurrence. NRG Oncology RTOG 9704 was the first phase 3 adjuvant pancreatic cancer trial to prospectively validate the prognostic value of postresection CA19-9 levels for overall survival (OS), with values of >90 and >180 associated with worse OS.[9] However, analysis of its predictability of pattern of disease recurrence, not limited to the first recurrence, in this setting of prospective evaluation and in associated contexts with SMS has not been performed and is the subject of this report.

Methods and materials

The study design of NRG Oncology RTOG 9704 has been previously reported in detail.[6,7] Protocol approval was received from the institutional review board at each study site, and informed consent was obtained from each patient prior to participation in the study. Patients with histologic proof of adenocarcinoma of the pancreas underwent potentially curative gross total resection of all disease. Specific protocol recommendations with regard to surgery and determination of surgical margin status were as follows: A standard Whipple or pylorus-preserving pancreaticoduodenectomy was preferred for lesions of the pancreatic

head (neck/uncinate process). The margins of the resected tissue (left lateral, bile duct), superior, and inferior were to be marked with metallic clips (when possible). If the tumor was adherent to and resected from adjacent structures (eg, a major blood vessel), small vascular or titanium clips were to be used to mark the margins of adherence. Also, resected specimens were to be marked with suture at sites of adherence so pathologists could determine whether radial margins were free of disease. In addition, the operative note and pathology report of each patient was centrally reviewed prior to patient registration by the study's surgical oncology principal investigator (J.P.H.). Patients were stratified at randomization according to documentation of tumor status at surgical margins as stated on the official pathology report. Therefore, strata included "negative," "positive," or otherwise not mentioned/commented on (ie, "unknown").

After stratification by SMS, nodal status, and tumor diameter, patients were randomly assigned to 1 of 2 treatment arms as depicted in eFigure 1; available as supplementary material online only at www.practical.radonc.org. All patients received adjuvant gemcitabine or 5-fluorouracil and chemoradiation therapy (CRT).

CA 19-9 testing

Lewis antigen expression is essential for expression of CA19-9; therefore, red cell phenotyping for Lewis A and B antigens was required for study eligibility and was obtained at each institution's laboratory. If patients were negative for both Lewis A and B antigens, they were considered CA19-9 nonexpressers. For patients who expressed either antigen, blood was drawn no more than 3 weeks before random assignment, or after random assignment but before the start of protocol treatment. Subsequently, serum was prepared, frozen at 20°C, and shipped (frozen) to the AAAA tissue bank, which was located at Latter-Day Saints Hospital. Centralized determination of CA19-9 was done using enzyme-linked immunosorbent assay GI-MA kits (Diagnostic Products Corporation, a Siemens Company; Gwynedd, United Kingdom). CA19-9 nonexpressing patients (Lewis antigen A and B negative) were assigned values of 0 because by definition, they did not have the ability to secrete CA19-9 into their serum.[10]

Statistical methods

The following baseline characteristics were dichotomized: primary tumor location (head vs everything else), pathologic T-stage (T1, T2 vs T3, T4), and American Joint Committee on Cancer stage (I, II vs III, IV). Race was categorized as white versus African American/other. Statistical comparisons to assess potential associations among baseline characteristics and 1) missing CA19-9 data, 2) CA19-9 levels, and 3) SMS were carried out using the χ^2 or Fisher's exact test. CA19-9 baseline expression was analyzed and grouped in 2 different ways (Lewis antigen negative vs CA19-9 < 180 vs CA19-9 ≥ 180 and Lewis antigen negative vs CA19-9 < 90 vs CA19-9 ≥ 90) with <180 and <90 as the reference levels. The CA19-9 cut points of 180 and 90 were used as in the previously published analysis[9] and based on previously published data from the Fox-Chase Cancer Center (180 cut point)[11] as well as the previously published adjuvant chemotherapy trial CONKO-001 (90 cut point).[3] CA19-9 was also analyzed as a continuous variable. SMS was analyzed as negative versus positive versus unknown (ie, no margin comment in pathology report; shown to have disease-free survival [DFS] and OS outcomes similar to negative-margin patients).[6] This variable was broken into 2 dummy variables with a value of negative as the reference level.

OS and DFS were estimated univariately with the Kaplan-Meier method,[12] and levels of CA19-9 and SMS were compared using the log-rank test. The first follow-up evaluation was required at 2 to 4 weeks after completion of chemoradiation and prior to the start of maintenance chemotherapy. Thereafter, follow-up examinations were required q 3 months for one year, then q 6 months for 2 years, then yearly and included use of abdominal computed tomography scans. Local relapse (LR) was defined as recurrence at the primary resection site; regional relapse (RR) was defined as recurrence in the regional lymph nodes associated with the primary resection site, local/regional relapse (LRR) combined both LR and RR, and all other disease relapses were defined as distant failure (DF). LR, RR, LRR, and DF were estimated by the cumulative incidence method,[13] and levels of CA19-9 and SMS were compared using Gray's test. LR, RR, LRR, and DF failures were counted regardless of when they occurred relative to each other. Only death was considered a competing risk for LR, RR, LRR, and DF. Univariate and multivariable Cox proportional hazards models[14] were used to identify the impact of CA19-9 and SMS on the OS, DFS, LR, RR, LRR, and DF. CA19-9 and SMS were forced into their respective models, and stepwise selection procedures were used to choose other variables using $\alpha = .05$ level as the entry and exit criteria for the model building. The following variables were assessed in the models along with CA19-9: treatment arm, age, sex, race, tumor location, nodal involvement, tumor diameter, and SMS. The same variables were assessed in the models for SMS with inclusion of CA19-9. To adjust for multiple comparisons, a P value ≤ .01 was considered statistically significant and >.01 to ≤ .05 a trend.

Results

The study opened on July 20, 1998 and closed on July 26, 2002 with a total of 538 patients. Of the 538 patients entered, 451 were eligible and analyzable for SMS. Of the

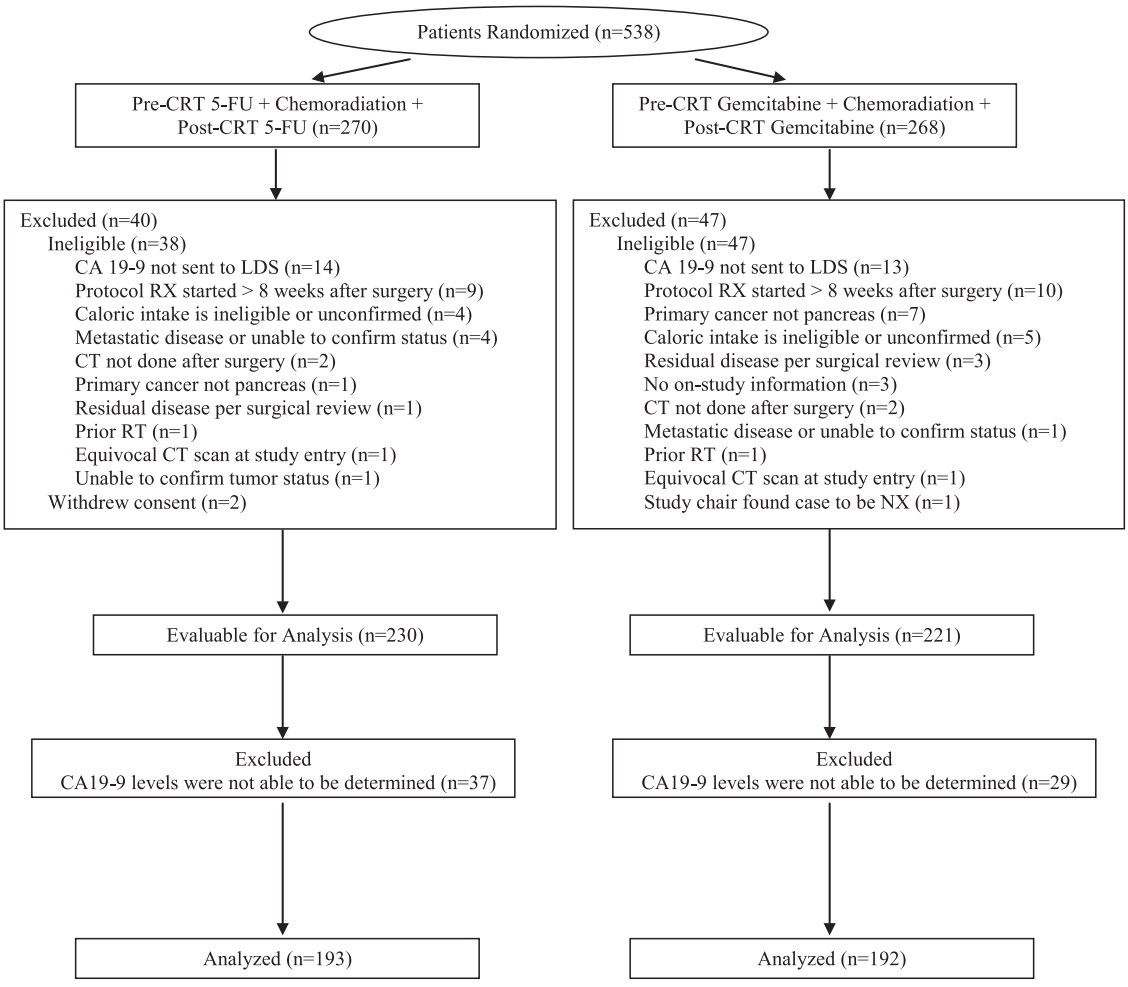

Figure 1 U.S. intergroup NRG Oncology RTOG 9704 phase 3 CONSORT diagram.

87 cases excluded, 85 were ineligible as detailed in the original report[6] and 2 withdrew their consent. Of the 451 eligible patients, 66 had no analyzable postresection CA19-9 data. These 66 patients were Lewis antigen–positive cases for whom tissue was sent to the AAAA tissue bank, per the protocol, but CA19-9 levels could not be determined. Therefore, the sample size for this analysis was 385. The CONSORT diagram is shown in Figure 1.

The median follow-up times were the same for both analysis groups: 1.48 years for all patients and 6.98 years for surviving patients (n = 73). Table 1 shows the pretreatment characteristics for patients entered into this study by the postresection CA19-9 value cut point of 90. No significant difference in pretreatment characteristics was observed by CA19-9 cut point grouping of 90. Results were similar at the CA19-9 180 cut point (220 patients <180, 33 ≥ 180), except that patients with ≥180 were more likely to have tumors ≥3 cm ($P = .048$). Patients with CA19-9 levels ≥90 or ≥180 were not more likely to be associated with a positive SMS compared with patients with values <90 or <180.

Table 2 shows the pretreatment characteristics of patients entered into this study by the SMS. Patients with positive SMS were more likely to have head of pancreas tumors, Karnofsky performance scores of 60 to 80, T3/T4/N1, American Joint Committee on Cancer stage III/IV disease, and primary tumor diameters of ≥3 cm.

eTable 1; available as supplementary material online only at www.practical.radonc.org shows the overall univariate analyses of disease recurrence for postresection CA19-9 value at the cut point of 90 and for SMS, with 4-year cumulative incidence reported. Postresection CA19-9 was associated with significant increases in both LRR (58% at ≥90 vs 44% at <90, $P = .012$; Fig 2A) and DF (89% at ≥90 vs 73% at <90, $P < .0001$; Fig 2B). Although these results did not meet the multiple comparisons adjusted P-value, a trend toward statistical significance for LRR was observed. In the gemcitabine treatment arm, this postresection CA19-9 association was significant for DF and not for LRR. In the 5-fluorouracil treatment arm, this postresection CA19-9 association was significant for both LRR and DF. These findings overall and by treatment arm were similar

Table 1 Pretreatment characteristics by CA19-9 (cut point = 90; n = 385)

	Lewis antigen–negative (n = 132)	<90 (n = 200)	≥90 (n = 53)	*P*-value[a]
Age (years)				
Median	60	63	62	
Range	37-82	35-84	39-78	
Sex				.45
Male	74 (56.1%)	116 (58.0%)	35 (66.0%)	
Female	58 (43.9%)	84 (42.0%)	18 (34.0%)	
Race				.16
White	119 (90.2%)	180 (90.0%)	43 (81.1%)	
Other	13 (9.8%)	20 (10.0%)	10 (18.9%)	
Primary location				.19
Head	117 (88.6%)	176 (88.0%)	42 (79.2%)	
Everything else	15 (11.4%)	24 (12.0%)	11 (20.8%)	
Karnofsky performance score				.13
60-80	51 (38.6%)	63 (31.5%)	24 (45.3%)	
90-100	81 (61.4%)	137 (68.5%)	29 (54.7%)	
T-stage				.13
T1, T2	23 (17.4%)	54 (27.0%)	12 (22.6%)	
T3, T4	109 (82.6%)	146 (73.0%)	41 (77.4%)	
N-stage (surgical)				.31
N0	37 (28.0%)	72 (36.0%)	18 (34.0%)	
N1	95 (72.0%)	128 (64.0%)	35 (66.0%)	
American Joint Committee on Cancer stage				.088
I, II	31 (23.5%)	69 (34.5%)	18 (34.0%)	
III, IV	101 (76.5%)	131 (65.5%)	35 (66.0%)	
Largest tumor dimension of primary				.21
<3 cm	56 (42.4%)	87 (43.5%)	16 (30.2%)	
≥3 cm	76 (57.6%)	113 (56.5%)	37 (69.8%)	
Primary tumor status				.70
Complete resection/negative margins	50 (37.9%)	80 (40.0%)	24 (45.3%)	
Complete resection/positive margins	51 (38.6%)	65 (32.5%)	17 (32.1%)	
Complete resection/unknown margins	31 (23.5%)	55 (27.5%)	12 (22.6%)	
Prescription				.86
Radiation therapy + 5-fluorouracil	64 (48.5%)	101 (50.5%)	28 (52.8%)	
Radiation therapy + gemcitabine	68 (51.5%)	99 (49.5%)	25 (47.2%)	

[a] *P*-value from χ^2 test.

at the postresection CA19-9 180 cut point. SMS was not associated with significant differences in LRR or DF (Figs 2C and D).

Table 3 shows the multivariable modeling of postresection CA19-9 value at the cut point of 90 for associations with survival and pattern of disease recurrence. In addition to being a predictor of OS and DFS, as previously reported,[9] postresection CA19-9 showed associations with LR, RR, LRR, and DF. Patients with CA19-9 ≥ 90 had a significant increased risk of LRR compared with patients with CA19-9 values of <90 ($P < .0001$; hazard ratio [HR]: 2.91; 95% confidence interval [CI], 1.90-4.46) and a significant increased risk of DF compared with patients with CA19-9 values of <90 ($P < .0001$; HR: 2.69; 95% CI, 1.92-3.77). Results were similar at the 180 cut point. eTable 2; available as supplementary material online only at www.practical.radonc.org shows the multivariable modeling of SMS for associations with survival and pattern of disease recurrence. On multivariable analysis, positive SMS was not associated with significant differences in LRR.

Although 90 and 180 are well-established cut points for CA19-9, these analyses were also conducted using CA19-9 as a continuous variable, which produced similar results.

Discussion

The primary objectives of the phase 3 NRG Oncology RTOG 9704 trial included a prospective evaluation of the ability of postresectional CA19-9 to predict survival among adjuvantly treated patients who had undergone a potentially curative resection for adenocarcinoma of the pancreas and the pattern of disease recurrence after adjuvant therapy. There are 2 major findings from this analysis: Postresection

Table 2 Pretreatment characteristics by surgical margin status (n = 385)

	Negative margins (n = 154)	Positive margins (n = 133)	Unknown margins (n = 98)	*P*-value[a]
Age (years)				
Median	61	61	63	
Range	38-84	36-80	35-82	
Sex				.24
Male	82 (53.2%)	82 (61.7%)	61 (62.2%)	
Female	72 (46.8%)	51 (38.3%)	37 (37.8%)	
Race				.13
White	131 (85.1%)	123 (92.5%)	88 (89.8%)	
Other	23 (14.9%)	10 (7.5%)	10 (10.2%)	
Primary location				.019
Head	125 (81.2%)	122 (91.7%)	88 (89.8%)	
Everything else	29 (18.8%)	11 (8.3%)	10 (10.2%)	
Karnofsky performance score				.0047
60-80	49 (31.8%)	62 (46.6%)	27 (27.6%)	
90-100	105 (68.2%)	71 (53.4%)	71 (72.4%)	
T-stage				< .0001
T1, T2	55 (35.7%)	9 (6.8%)	25 (25.5%)	
T3, T4	99 (64.3%)	124 (93.2%)	73 (74.5%)	
N-stage (surgical)				.12
N0	52 (33.8%)	36 (27.1%)	39 (39.8%)	
N1	102 (66.2%)	97 (72.9%)	59 (60.2%)	
American Joint Committee on Cancer stage				.025
I, II	50 (32.5%)	30 (22.6%)	38 (38.8%)	
III, IV	104 (67.5%)	103 (77.4%)	60 (61.2%)	
Largest tumor dimension of primary				.0003
<3 cm	82 (53.2%)	40 (30.1%)	37 (37.8%)	
≥3 cm	72 (46.8%)	93 (69.9%)	61 (62.2%)	
CA19-9				.70
Lewis antigen-negative	50 (37.9%)	80 (40.0%)	24 (45.3%)	
<90	51 (38.6%)	65 (32.5%)	17 (32.1%)	
≥90	31 (23.5%)	55 (27.5%)	12 (22.6%)	
Prescription				.35
Radiation therapy + 5-fluorouracil	84 (54.5%)	64 (48.1%)	45 (45.9%)	
Radiation therapy + gemcitabine	70 (45.5%)	69 (51.9%)	53 (54.1%)	

[a] *P*-value from χ^2 test.

CA19-9 predicts for pattern of disease recurrence after adjuvant therapy, inclusive of both LRR and DF, whereas SMS is only associated with DF. Although SMS and postresection CA19-9 levels have been described as prognostic factors for survival in patients with pancreatic carcinoma who are able to undergo surgical resection,[9,15,16] the findings in this report challenge the commonly held beliefs that SMS and elevated postresection CA19-9 levels are the major predictors of primarily LRR and DF, respectively. These findings could greatly influence the prioritization and/or timing of adjuvant chemotherapy and/or RT.

NRG Oncology RTOG 9704 was the first phase 3 trial to perform a prospective analysis of postresection CA 19-9 levels in patients treated with adjuvant CRT. The trial demonstrated that in the postoperative setting, postresection CA 19-9 levels were the most important predictor of OS. Patients with CA19-9 of ≥180 had a median survival of 9 months, compared with 21 months for those with CA 19-9 < 180 ($P < .0001$; HR: 3.58). At the cut point of 90, as used for eligibility for the phase 3 adjuvant CONKO-0001 trial (only patients with values <90 were allowed in the trial), the median survival time for patients with CA 19-9 ≤ 90 was 23 months, whereas patients with CA 19-9 > 90 had a median survival of 10.4 months ($P < .0001$; HR: 3.34).[9]

These findings became the basis for stratification of patients within the successor, and currently active, YYYY adjuvant phase 3 trial. In this study, patients are stratified at the postresection CA19-9 cut point of 90, and patients with values >180 are ineligible. Although the primary analysis of NRG Oncology RTOG 9704 demonstrated that >70% of patients developed DF and approximately 30% LRR at the time of the first relapse of disease, the pattern of disease recurrence potentially associated with postresection CA19-9

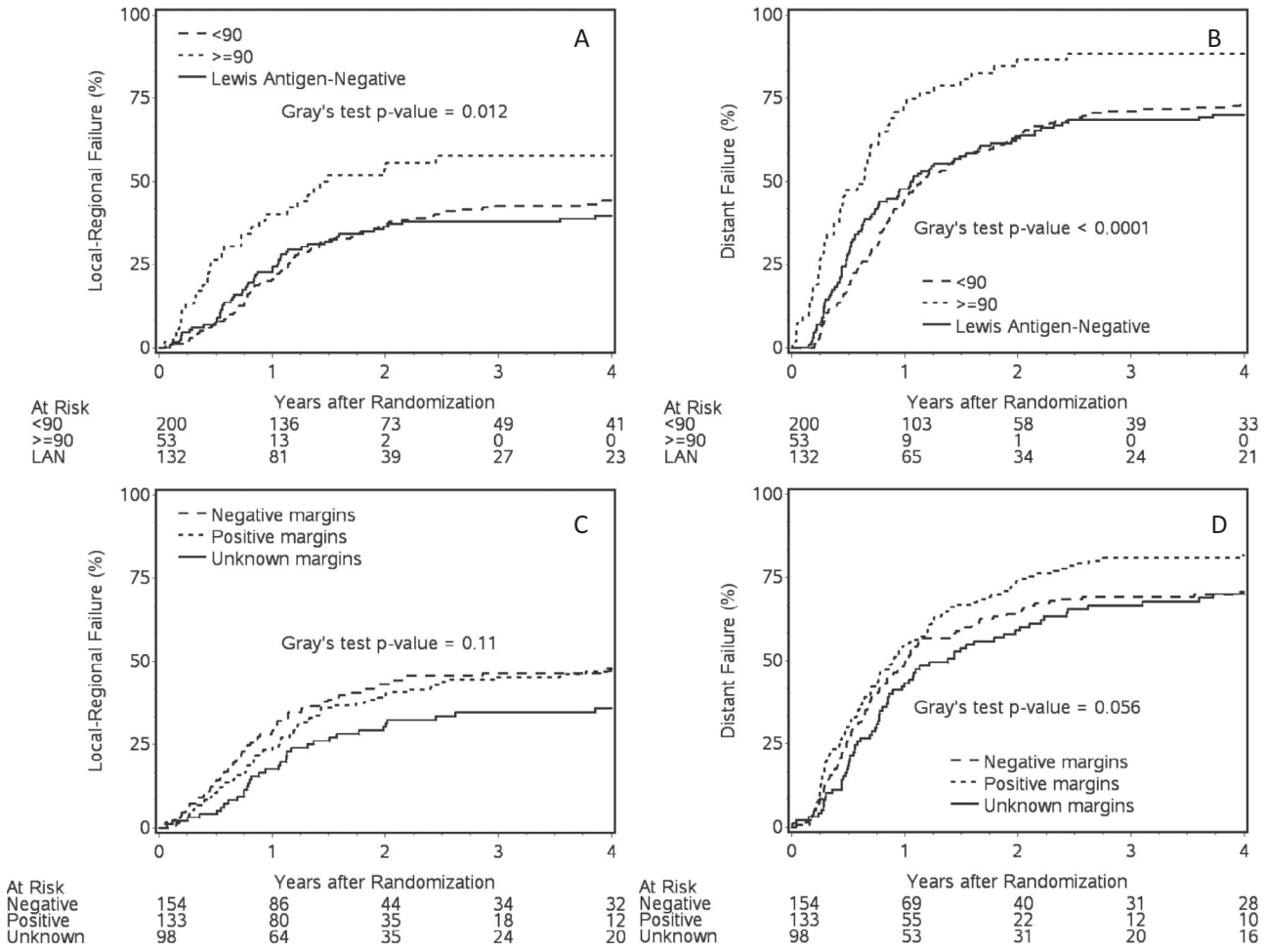

Figure 2 (A) Local–regional failure by CA19-9; (B) distant failure by CA19-9; (C) local-regional failure by surgical margin status; and (D) distant failure by surgical margin status.

levels had not been evaluated.[6,7,9] Postresection elevation in CA19-9 is often presumed to be primarily a predictor of DF without consideration of the associated potential for LRR. Although the report of this analysis supports the association with DF, the findings have also demonstrated that such an elevation in CA19-9 levels is associated with LRR at a similar magnitude. In addition, patients with postresection CA19-9 levels ≥90 had an almost 3-fold increase in LRR compared with those with postresection CA19-9 levels of 90.

Postresection SMS has been reported in large institutional series to be a significant and independent predictor of survival.[15,16] However, this observation has not been routinely demonstrated in prospective phase 3 trials evaluating use of adjuvant therapy. In fact, in the 3 randomized trials that have demonstrated at least a suggested benefit in survival with the use of adjuvant therapy, SMS was not found to be an independent predictor of survival.[3-7] In addition, evaluation of SMS on its association with pattern of disease recurrence in a large institutional series and in the setting of prospective adjuvant phase 3 trials has not been routinely reported.[3-8,15,16] Among patients with a postresection positive SMS, LRR is typically presumed to be a significant contributor to the pattern of disease recurrence.

Furthermore, the presence of positive SMS is often, in part, the basis for recommendation of adjuvant RT[15,16] and is used as the rationale for consideration of RT dose escalation.[17,18] This report challenges the utility of the use of postresection SMS as a predictor of LRR and as a basis for the use of RT or RT dose escalation in the setting of available postresection CA19-9 levels. Positive SMS has been previously demonstrated to not be an independent predictor of patient survival,[6,7] with NRG Oncology RTOG 9704 being the first phase 3 trial that required central RT quality assurance review.[19] The current analysis demonstrates that in the setting of central RT quality assurance, positive SMS is also not an independent predictor of LRR. In addition, evaluation of SMS in the setting of available postresection CA19-9 levels as performed in this report demonstrates that postresection CA19-9 was the only independent predictor of both LRR and DF.

Table 3 Stepwise multivariable Cox proportional hazards models: CA19-9 forced into modals (n = 385)

Endpoint	Adjustment variables	Comparison	Adjusted HR[a]	95% CI LL	95% CI UL	*P*-value*
LR	CA19-9	Lewis antigen–negative	0.90	0.61	1.32	.57
		<90	1.00	–	–	–
		≥90	2.59	1.59	4.21	.0001
	Age	Continuous	0.98	0.96	0.99	.021
	Surgical margin status	Negative	1.00	–	–	–
		Positive	1.00	0.69	1.46	.99
		Unknown	0.55	0.34	0.87	.012
RR	CA19-9	Lewis antigen–negative	1.19	0.72	1.95	.50
		<90	1.00	–	–	–
		≥90	4.06	2.24	7.33	< .0001
	Nodal involvement	No	1.00	–	–	–
		Yes	1.65	1.01	2.70	.045
LRR	CA19-9	Lewis antigen–negative	0.96	0.68	1.36	.82
		<90	1.00	–	–	–
		≥90	2.91	1.90	4.46	< .0001
	Age	Continuous	0.98	0.97	0.99	.031
	Sex	Female	1.00	–	–	–
		Male	1.38	1.01	1.90	.045
	Surgical margin status	Negative	1.00	–	–	–
		Positive	0.99	0.71	1.39	.95
		Unknown	0.63	0.42	0.95	.025
DF	CA19-9	Lewis antigen–negative	0.98	0.75	1.27	.86
		<90	1.00	–	–	–
		≥90	2.69	1.92	3.77	< .0001
	Surgical margin status	Negative	1.00	–	–	–
		Positive	1.31	1.00	1.70	.048
		Unknown	0.84	0.62	1.13	.25
OS	CA19-9	Lewis antigen–negative	1.27	0.99	1.62	.06
		<90	1.00	–	–	–
		≥90	3.42	2.47	4.73	< .0001
	Race	White	1.00	–	–	–
		African-American/other	1.53	1.10	2.14	.012
	Nodal involvement	No vs yes	1.51	1.18	1.93	.0011
DFS	CA19-9	Lewis antigen–negative	1.15	0.91	1.45	.26
		<90	1.00	–	–	–
		≥90	2.82	2.05	3.87	< .0001

CI, confidence interval; DF, distant failure; DFS, disease-free survival; HR, hazard ratio; LL, lower limit; LR, local relapse; OS, overall survival; LRR, local/regional recurrence; RR, regional relapse; UL, upper limit.

[a] A hazard ratio of 1 indicates no difference between the 2 subgroups.

* *P*-value from χ^2 test using the Cox proportional hazards model.

Conclusions

In this unique adjuvant setting of a prospective evaluation of postresection CA19-9 levels, CA19-9 has significant association with both LRR and DF that was not seen with SMS. These findings contradict the commonly held presumption that an elevation in postresection CA19-9 levels reflects the development of distant disease spread of pancreatic cancer without consideration of LRR. These findings support consideration of adjuvant RT dose intensification among patients with elevated postresection CA19-9.

Supplementary data

Supplementary material for this article (https://doi.org/10.1016/j.adro.2018.01.003) can be found at www.practicalradonc.org.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9-29.

2. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg*. 1985;20:899-903.
3. 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;297:267-277.
4. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer. *JAMA*. 2013;310:1473-1481.
5. 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;350:1200-1210.
6. Regine WF, Winter K, 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;299:1019-1026.
7. Regine WF, Winter K, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or flourouracil chemotherapy following resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol*. 2011;18:1319-1326.
8. 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;230:776-782.
9. Berger AC, Garcia M, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol*. 2008;26:5918-5922.
10. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res*. 1987;47:5501-5503.
11. Montgomery RC, Hoffman JP, Riley LB, et al. Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. *Ann Surg Oncol*. 1997;4:551-556.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
13. Kalbfleish JD. *The Statistical Analysis of Failure Time Data*. New York: John Wiley & Sons; 1980.
14. Cox DR. Regression models and life-tables. *J Roy Statist Soc*. 1972;34:187-202.
15. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol*. 2008;26:3503-3510.
16. Chang DK, Johns AL, Merrett ND, et al. Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol*. 2009;27:2856-2862.
17. Willett CG, Lewandrowski K, Warshaw AL, Efird J, Compton CC. Resesection margins in carcinoma of the head of the pancreas implications for radiation therapy. *Ann Surg*. 1993;217:144-148.
18. Rwigema JC, Heron DE, Parikh SD, et al. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer*. 2012;43:70-76.
19. Abrams RA, Winter KA, Regine WF, et al. Failure to adhere to protocol specified radiation therapy guidelines was associated with decreased survival in RTOG 9704—a phase iii trial of adjuvant chemotherapy and chemoradiotherapy for patients with resected adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys*. 2012;82:809-816.