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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

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Abstract

Purpose—In RTOG 9704, as previously published, patients with resected pancreatic adenocarcinoma received continuous infusion 5-FU and concurrent radiotherapy (5FU-RT). 5FU-RT treatment was preceded and followed by randomly assigned chemotherapy, either 5-FU or gemcitabine. This analysis explored whether failure to adhere to specified RT guidelines influenced survival and/or toxicity.

Methods and Materials—RT requirements were protocol specified. Adherence was scored as per protocol (PP) or less than per protocol (<PP). Scoring occurred following therapy but prior to trial analysis and without knowledge of individual patient treatment outcomes. Scoring was done for all tumor locations and for the subset of pancreatic head location.

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Conflict of Interest Statement none

Results—RT was scored for 416 patients: 216 PP and 200 <PP. For all pancreatic sites (head, body/tail) median survival (MS) for PP vs. <PP was 1.74 vs. 1.46 years (log-rank $p=0.0077$). In multivariate analysis, PP vs. <PP score correlated more strongly with MS than assigned treatment arm ($p=0.014$, $p=NS$, respectively); for patients with pancreatic head tumors, both PP score and gemcitabine treatment correlated with improved MS ($p=0.016$, $p=0.043$, respectively). For all tumor locations PP score was associated with decreased risk of failure ($p=0.016$) and, for gemcitabine patients, a trend toward reduced grade 4/5 non-hematologic toxicity ($p=0.065$).

Conclusions—This is the first phase III, multi-center, adjuvant protocol for pancreatic adenocarcinoma to evaluate the impact of adherence to specified RT protocol guidelines on protocol outcomes. Failure to adhere to specified RT guidelines was associated with reduced survival and, for patients receiving gemcitabine, trend toward increased non-hematologic toxicity.

Keywords

Radiotherapy; quality assurance; pancreatic adenocarcinoma; adjuvant therapy; chemoradiotherapy

INTRODUCTION

Radiotherapy (RT) combined with chemotherapy and surgery is efficacious in the management of gastrointestinal carcinoma, especially of the rectum and stomach (1–4). However, whether an adjuvant paradigm involving both RT and chemotherapy, or chemotherapy alone, represents the best option for patients with curatively resected pancreatic adenocarcinoma is controversial (5–9). Randomized trials have demonstrated an advantage to surgery followed by gemcitabine chemotherapy as compared to surgery alone (6) and have also raised the question that radiotherapy, rather than being helpful, might actually be detrimental (5).

The administration of RT involves numerous clinical and technical details and the extent to which adherence to protocol specified guidelines influences treatment outcomes has not been well studied. MacDonald et al (4) have reported that in INT 0116, an adjuvant trial for resected gastric adenocarcinoma, initially submitted RT fields were judged inappropriate because of inadequate coverage of at risk areas for sub-clinical tumor or because of unacceptable toxicity risk in 35% of patients. Moreover, deviations from protocol specified RT guidelines are known to occur in cooperative group trials during protocol management (10,11).

Because deviations from established QA guidelines had been shown to impact on survival in a number of non-oncologic clinical contexts (12–15) and because of the existing controversy regarding the role of RT in the adjuvant management of pancreatic adenocarcinoma, the following secondary analysis of RTOG 9704 was undertaken.

METHODS

RTOG 9704

The details of this protocol have been previously published (16). Eligibility included adenocarcinoma of the pancreas and gross total tumor resection with curative intent. All patients gave written, protocol specific, informed consent according to institutional and federal guidelines.

Treatment

Patients were randomly assigned to pre and post chemoradiotherapy (CRT) 5-FU (arm 1) or gemcitabine (arm 2). Randomization was performed at registration and was stratified for tumor diameter (< 3 cm vs. $\geq$ 3 cm), nodal status (negative vs. positive) and surgical margins (negative vs. positive vs. unknown). Pre-CRT chemotherapy in arms 1 and 2 consisted of continuous infusion 5-FU (250 mg/sq m/day for 3 weeks) or gemcitabine (1000 mg/sq m weekly for 3 weeks), respectively. Between 1–2 weeks after completion of pre-CRT chemotherapy, CRT was initiated and the same for both arms. CRT consisted of 50.4 Gy in 28 fractions, 5 days per week with continuous infusion 5-FU, 250 mg/m²/day throughout RT. Post-CRT chemotherapy was initiated 3–5 weeks after completion of CRT; arm 1 consisted of 3 months of continuous infusion 5-FU (250 mg/sq m/day 4 weeks out of 6) and arm 2 consisted of three months of gemcitabine (1000 mg/sq m weekly, 3 weeks out of 4) (Figure 1A).

Treatment volume included the tumor bed and regional lymph nodes as defined by preoperative computed tomographic (CT) imaging (16). After an initial dose of 45 Gy, the final 5.4 Gy dose was limited to the preoperative tumor bed. Minimum, nominal photon treatment energy was 4 MV and a minimum of 3–4 fields were required with all fields treated daily. Critical normal organ dose limitations were:

- 1) < 60% of hepatic volume receiving > 30Gy,
- 2) The equivalent of at least two thirds of one kidney spared from all RT fields, and
- 3) spinal cord maximal dose limited to $\leq$ 45Gy.

Submission of materials for prospective quality assurance (QA) of RT was requested, including submission of preoperative abdominal CT scan with pre-operative GTV indicated along with the planned RT fields and reports describing pathologic and operative findings.

Radiotherapy QA scoring

RTOG 9704 specified the following details for planning and executing RT per protocol: simulation, use of simulation films and port film verification, clinical target volume definition, critical normal organs and coverage limitations, time dose fraction scheme, acceptable and unacceptable treatment interruptions, treatment beam energy and source to axis distance, field arrangements, initial and boost field design parameters, criteria for blocking normal organs and tissues, need for isodose planning, and range of acceptable dose heterogeneity. The protocol further provided criteria for scoring these various components of RT as per protocol, variation acceptable, and variation unacceptable (Table 1). Final RT QA review was undertaken as cases were assessed and after all necessary source materials were submitted, accessioned, and organized at RTOG headquarters. At the end of 2001, when it was realized based on the first 216 case reviews that some variations in requested field margins which had been anticipated to increase risk of toxicity were not producing increased toxicity, the definition of variation acceptable was liberalized. Specifically, larger margins into normal tissue were allowed as long as they did not compromise normal organ tolerance requirements. This change was approved prior to implementation by the radiotherapy principal investigators (RAA, WR), the chair of the gastrointestinal committee (CW), the protocol statistician (KW), and the chair and co-chair of the RTOG. All RT QA review was completed by the end of calendar year 2003 and prior to any analysis or knowledge of patient survival by treatment assignment. The process of review was a two step process. In the first step, one of the RT principle investigators (RAA or WFR) reviewed the submitted materials. If the RT was scored as per protocol (PP), no further review was undertaken and this score was assigned. If the RT was scored as less than per protocol

(<PP), then the other RT principle investigator also reviewed the materials to confirm the scoring. Disagreement between the two reviews was rare and resolved by discussion.

Cases where the RT was not completed or where the necessary materials were not submitted were not considered for RT QA analysis.

Statistics

This was a secondary analysis comparing survival outcome by RT QA review category for all patients enrolled. Separate consideration of pancreatic head patients was in line with prospectively planned survival analysis of these patients based on differences in surgical management between patients with tumors of the pancreatic head region (pancreaticoduodenectomy) and body tail region (distal pancreatectomy/splenectomy) and the fact that approximately 80% of patients were expected to have tumors arising in the pancreatic head region. Initially, there were four categories: Per Protocol, Acceptable Deviation, Unacceptable Deviation, and Incomplete/Not Evaluable. Incomplete/Not Evaluable were excluded from further analysis. Because of relatively small patient numbers in the Unacceptable Deviation category (5–6%), this category and acceptable deviation were collapsed into a single category of “less than Per Protocol (<PP)”. Overall survival was estimated univariately with the Kaplan-Meier method and differences were tested using the log-rank test. Reported median survival times (MS) are the times (in years) at which the estimated survival rate reached 50%. Multivariate analyses were performed with Cox proportional hazard models (17) to see if there was an association between RT QA review (PP and <PP) and outcome endpoints after adjusting for treatment arm (RT+Gemcitabine vs. RT+5-FU) and for the stratification variables of nodal involvement (no vs. yes), tumor diameter (< 3 vs. ≥ 3 cm) and margin status (negative vs. positive and negative vs. unknown). Z-tests were used to test for differences in binomial proportions of acute (≤ 90 days from the end of treatment) toxicities (hematologic, non-hematologic) between PP vs. <PP status. Finally, correlation was sought between institutional enrollment and frequency of PP and <PP status. This was examined in two ways: First, by defining institutional enrollment into this protocol as low (1–3), medium (4–5), and high (6 or more) over the entire period during which the protocol was open, and by looking for a trend in RTQA score using the Wilcoxon log-rank test; secondly, we compared institutions enrolling less than 1 patient per year to those enrolling 1 or more patients per year. Initial analysis of protocol results was completed and performed in 2007 at which time median follow up on all patients was 1.5 years and 4.7 years on surviving patients (16). This report reflects a re-analysis performed in June 2010 with 81% of all patients dead and with median follow up of 7 years for surviving patients.

Result

Enrollment and Eligibility—RTOG 9704 accrual opened and closed on 7/20/98 and 7/26/2002, respectively, with 538 patients enrolled; 270 on the 5-FU arm and 268 on the gemcitabine arm. Of these, 451 were eligible and analyzable (16). Figure 1B charts patient numbers for each step of this analysis

RT Compliance

Final RT QA Review—Thirty-five patients had incomplete or inevaluable radiotherapy data, 19 in the 5-FU arm and 16 in the gemcitabine arm. Reasons for being incomplete / inevaluable included: death after enrollment but before the completion of radiotherapy – 2 patients, disease progression – 4 patients, refusal of radiotherapy – 7 patients, radiotherapy not begun – 8 patients, and insufficient data submitted – 14 patients (Figure 1B).

Of the remaining 416 patients, 216 (52%) had radiotherapy QA scores that were per protocol (PP) and 200 (48%) had radiotherapy QA scores that were less than per protocol (< PP) (Figure 1B). The reasons for being < PP and their frequency are given in Table 2. The radiotherapy QA scores for both treatment arms and for the all site and pancreatic head site analyses are shown in Table 3. PP and < PP patients did not differ by Demographics or identified prognostic variables (Table 4)

Protocol Survival and Causes of Death—For all patients, MS on the 5-FU arm was 1.43 years and, on the gemcitabine arm, 1.55 years (log-rank $p=0.51$, Figure 2A). For patients with head of pancreas tumors MS was 1.43 and 1.71 years, respectively ($p=0.12$, Figure 2C). The causes of death for evaluable patients on the 5-FU arm were: cancer 88%, treatment 0%, unrelated to cancer or treatment 7%, second malignancy 1%, and unknown 4%; for the gemcitabine arm the causes of death for evaluable patients were: cancer 80%, treatment 1%, unrelated to cancer or treatment 9%, second malignancy 3%, and unknown 7%.

Pretreatment Review of Radiotherapy Fields—Information including pathology report, operative note, and preoperative imaging in conjunction with treatment planning images showing isocenter, field edges, and blocking was requested to be submitted to RTOG Headquarters in a timely fashion for pretreatment review and possible correction. Although the requested treatment planning films were generally submitted, this attempted prospective review, which was not an absolute requirement for eligibility, most often failed to occur because the other necessary documentation did not arrive at RTOG Headquarters within the necessary time frame.

Correlations Among Survival, Failure and RT QA Score—When all analyzable patients are considered, the RT QA score of PP and <PP yielded MS of 1.74 years and 1.46 years, respectively, log-rank $p=0.0077$ (Figure 2B). Having an RT QA Score of PP was associated with MS numerically superior to that seen with either treatment arm (Figures 2A and 2B). For the patient subset with head of pancreas tumors the PP and <PP MS were 1.74 and 1.48 years, respectively (log-rank $p=0.026$) and again the MS for PP patients was numerically superior to that seen with either treatment arm (Figures 2C and 2D). As previously reported, (16) factors in RTOG 9704 that correlated with survival in multivariate analysis included nodal status ($p=0.001$) and tumor size ($p=0.047$) for all patients and for head of pancreas patients, only nodal status ($p=0.003$). When the impact of RT QA score on survival was added to the multivariate analysis for all patients, nodal status and tumor size remain significant and RT QA score is also significant ($p=0.0022$, $p=0.025$, and $p=0.014$, respectively). When RT QA score was added to the multivariate analysis for head of pancreas patients, treatment arm, nodal status and RT QA score were all found to be significant ($p=0.043$, 0.0036 , and 0.016 , respectively). These results are shown in Table 5. The effect of factoring in the multivariate analysis on survival by treatment arm is shown graphically in Figure 3 for the pancreatic head patients and shows a significant difference in survival by treatment arm ($p=0.04$).

As shown in Table 6, PP radiotherapy QA score was associated with the occurrence of first failure significantly less often than having < PP radiotherapy score ($p=0.016$). First failure as isolated local regional failure occurred in only 59 patients. Of these, 49% were associated with <PP RT score and 51% with PP RT score ($p=0.86$).

Neither surgical review score nor chemotherapy review score correlated with RT QA status or survival. (Data not shown).

Effect of RT QA score on observed acute toxicity (Grade 3 or worse)

There was no significant difference in toxicity in the 5-FU arm when analyzed by RTQA score. However, in the Gemcitabine arm there was a trend toward increased toxicity for the <PP patients for both hematologic grade 4 ($p=0.08$) and non hematologic toxicity ($p=0.06$) (Table 7). Of the patients experiencing grade 4 or 5 toxicity on the gemcitabine arm with a score of <PP only one of these had an RTQA score of deviation unacceptable.

Effect of Institutional Enrollment Volume on RT QA score

One hundred and fifty nine institutions enrolled patients in this trial. The median patient enrollment per institution per year was 0.5; i.e. 2 patients over the course of the study. No correlation with RT QA score was seen by number of patients enrolled per institution or by whether an institution enrolled more or less than one patient per year.

Discussion

The Agency for Healthcare Quality Research has defined quality in healthcare as “..... doing the right thing, at the right time, in the right way, for the right person—and having the best possible results” (18). In this secondary analysis from RTOG 9704, we have observed that radiotherapy was not always administered in the prospectively defined “right” way, and when it was not, the treatment administered was associated with inferior survival (Figures 2B, 2D) and was more likely to result in the occurrence of first failure ($p=0.016$) (Table 6).

For the gemcitabine arm deviation from recommended radiotherapy guidelines resulted in a trend toward increased acute toxicity, especially non-hematologic toxicity. Gemcitabine is a significantly more potent radiosensitizing agent than 5-FU and is also associated with radiotherapy recall (19,20). The frequency of these deviations is consistent with the those seen in the German Hodgkins Disease Study Group for Study HD-10 (where radiotherapy was rated as suboptimal in 47% of cases) (21), as well as in a number of other oncologic and non-oncologic studies (4,10,11,14).

Additionally: 1. The impact on survival of a radiotherapy QA score of < PP remained significant upon multivariate analysis (Table 5) 2. Arithmetically, the magnitude of effect on survival of RT QA score by itself was larger than that of treatment by itself (Figures 2A–D). Moreover, when the effect of RT QA score was taken into account by multivariate analysis, along with nodal involvement, this improved the precision of the estimate of the treatment effect between the two treatment arms and survival differences between the 2 treatment arms became significantly different for pancreatic head patients (Figure 3).

We acknowledge that post treatment review can document but not prevent radiotherapy protocol variations. A mandated, rapid and efficient prospective method of review and intervention, as in now done through the Advanced Technology Committee of the RTOG, is required to prevent their inclusion in actual treatment (for more information please see www.rtog.org and/or <http://atc.wustl.edu/>). With this lesson in mind the current RTOG/SWOG/EORTC protocol for the adjuvant therapy of pancreatic adenocarcinoma (RTOG 0848) includes real time, prospective, mandated review and correction of deviations prior to the start of radiotherapy.

These observations result from a planned secondary analysis rather than a prospective assignment. There is no other way to study this issue ethically.

To our knowledge this analysis represents the first well documented association that radiotherapy quality, as defined by adherence to protocol specified guidelines, and survival may be strongly correlated in the management of any gastrointestinal malignancy, although

our results relate specifically to pancreatic cancer. Speculatively, failure to fully appreciate this in past trials, may have contributed to the current uncertainty and controversy regarding the role of radiotherapy in this context (24).

Although at the time we set out to examine these QA issues we were aware of accumulating experiences in more general medical situations that correlated guideline adherence with survival (12–15). More recently, data have also become available from studies in oncologic contexts, both related and not related to the details of radiotherapeutic management, that confirm and reinforce the role of protocol adherence for optimal survival (23,25–27).

It is acknowledged that radiation protocol violations could be associated with inferior survival without being the causative factor for inferior survival. Other possible associations with survival within these data were sought and not found.

Our data raise a number of questions. One of these is the mechanism by which QA deviation in radiotherapy might result in this outcome. To our minds, the most logical, possible explanation is that local regional radiotherapy is important for optimal survival in the context of adjuvant therapy for pancreatic adenocarcinoma. RTOG 9704 was designed from this perspective and both arms of management included radiation management. While acknowledging that the role of radiotherapy in this context has become more controversial since RTOG 9704 was designed over 13 years ago, it remains possible that this hypothesis is correct. RTOG 0848 has recently opened and is designed to address this question. That local regional radiotherapy would be important is consistent with some but not all reports examining this question (reviewed in ref 9) and also consistent with the results of two randomized trials comparing radiotherapy plus chemotherapy to chemotherapy alone for locally unresectable patients (28,29) and with data indicating that uncontrolled local regional disease is a frequent cause of death in pancreatic cancer (30).

If radiotherapy is important for optimal survival, then inferior radiotherapy could logically be associated with inferior survival outcomes (23). The appearance of the observed survival difference between PP and <PP treatment at 12 and 18 months (Figures 2B, 2D) mitigates against the cause being either acute or late radiotherapy toxicity. Additional support for our results can be inferred from: For malignancies with high frequencies of both nodal involvement and distant failure, a number of randomized, phase III trials have confirmed a survival advantage to chemotherapy and radiotherapy versus chemotherapy only (1,31–36). Variation in surgery when done for local regional tumor management has also been documented to adversely impact on survival for a variety of tumors including pancreatic adenocarcinoma (37,38). Because these differences generally correlate with operative experience or volumes, we looked for, but did not find, an association between outcome and number of patients enrolled per institution in our data.

A priori, one might expect that deviation from required radiotherapy parameters would have produced an increased incidence of first failure within the irradiated volume. However in both breast cancer and prostate cancer regional involvement often manifests first as systemic rather than regional failure (39,40). Therefore, failure to identify a first failure difference within the irradiated volume of pancreatic cancer patients does not mitigate against the validity of our data, especially for a tumor where local regional failure patterns may be difficult to assess.

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A PHASE III STUDY OF PRE AND POST CHEMORADIATION 5-FU VS. PRE AND POST CHEMORADIATION GEMCITABINE FOR POSTOPERATIVE ADJUVANT TREATMENT OF RESECTED PANCREATIC ADENOCARCINOMA

SCHEMA	
S <u>Nodal Status</u>	R
1. Uninvolved	<u>Arm 1:</u> Pre-CRT + Chemoradiation (CRT) + Post-CRT
T 2. Involved	A 5-FU (5-FU/RT) 5-FU
R <u>Tumor Diameter</u>	N
1. < 3 cm	D
A 2. ≥ 3 cm	O <u>Arm 2:</u> Pre-CRT + Chemoradiation (CRT) + Post-CRT
T <u>Surgical Margins</u>	M Gemcitabine (5-FU/RT) Gemcitabine
1. Negative	I
I 2. Positive	Z
3. Unknown	E
F	
Y	

Figure 1A.
Treatment Schema For RTOG Protocol 9704

RTOG 9704 Patient Flow for This Analysis

Figure 1B.
Consort Diagram

Patients at Risk

RT + 5-FU
 RT + Gemcitabine

230	160	81	52	46	43	33	20
221	155	88	59	45	41	34	22

Patients at Risk

< Per Protocol
 Per Protocol

200	145	71	43	31	27	24	18
216	154	93	64	56	54	40	21

Figure 2.**Survival Results**

2A. Survival Results By Randomization Between Treatment Arms. There is no significant difference in survival between the two treatment arms. Median Survivals: 5FU arm = 1.43 years; gemcitabine arm = 1.55 years ($p=0.51$)

2B. Survival Results By Radiotherapy Quality (RTQA) Score as Per Protocol (PP) or less than Per Protocol (<PP). Patients with RTQA score of PP had significantly better survival; 1.74 years vs. 1.46 years ($p=0.0077$).

2C. Survival Results For **Head of Pancreas** Patients By Treatment Arm. There is a trend towards improved survival ($p=0.12$) favoring the gemcitabine arm for head of pancreas patients. (median survivals: 5FU arm = 1.43 years, gemcitabine arm = 1.71 years).

2D. Survival Results For Head of Pancreas Patients By RTQA Score. Patients with RTQA score of PP had significantly better survival; 1.74 years vs. 1.48 years ($p=0.026$).

Patients at Risk								
RT + 5-FU	186	133	68	42	36	33	24	15
RT + Gemcitabine	173	130	75	51	38	35	28	18

Figure 3. Survival Results for head of pancreas patients by treatment when the results of factors significant in multivariate analysis are considered (RTQA Score and nodal involvement).

Table 1

Criteria For Assessing Radiotherapy

Field Size Parameters			
Initial Fields (180 to 4500 cGy)	Per Protocol	Variation Acceptable	Variation Unacceptable
AP/PA FIELDS			
a) Length	4–5 Vertebral Bodies (V.B.)		< 4 or > 5 V.B.
b) Distance from Primary Tumor Bed	2 – 3 cm	1 cm to < 2 cm > 3 cm to < 4 cm	< 1 cm or > 4 cm
c) Distance From V.B. Edge	2 cm	1 cm to < 2 cm > 2 cm to < 3 cm	< 1 cm or > 3 cm
LATERAL FIELDS			
a) Length	Same as for AP/PA Fields		
b) Distance from anterior tumor bed	1.5 cm – 2 cm	0.5 cm to < 1.5 cm > 2 cm to 3 cm	< 0.5 cm or > 3 cm
c) Distance from Rest of Tumor Bed	2 cm – 3 cm	1 cm to < 2 cm > 3 cm to 4 cm	< 1 cm or > 4 cm
d) Posterior Edge	Mid V.B.	Within 1cm of mid V.B.	> 1 cm away from mid V.B.
e) Distance from Anterior field edge to V.B.	3.5 cm to 4 cm	2.5 cm to < 3.5 > 4cm to 5 cm	< 2.5 cm or > 5 cm
BOOST FIELDS (4680–5040cGy)			
Distance From Tumor Bed	1.5 cm to 2 cm	1 cm to < 1.5 cm > 2 cm to 3 cm	< 1 cm or > 3 cm

Other Parameters			
	Per protocol	Variation Acceptable	Variation Unacceptable
Dose delivered	+/- 5%	Not within +/- 5% Within +/- 10%	Not within +/- 10%
Elapsed Time	< 7 days break	8–14 days break	> 14 days break

Table 2

Variations and Their Frequency in the 200 Patients with < Per Protocol Radiotherapy (Total variations are more than 200 as some patients had more than one variation)

Variation	Initial Treatment or Boost Treatment	Frequency
Field Placement or Size	Initial	140
Dose Administered	Initial	14
Dose per Fraction	Initial	6
Elapsed Treatment Time	Initial	26
Field Placement or Size	Boost	127
Dose Administered	Boost	12
Dose per Fraction	Boost	3
Elapsed Treatment Time	Boost	14

Table 3

RT QA score By Treatment Arm and Tumor Location

	RT + 5-FU		RT + Gemcitabine		Total	
All Pancreatic Tumors (Head and Body/Tail)	211 (100.0%)		205 (100.0%)		416 (100.0%)	
	n	%	n	%	n	%
PP	117	55.4	99	48.3	216	51.9
<PP	94	44.6	106	51.7	200	48.1

Pancreatic Head Tumors (Not Body/Tail)	186 (100.0%)		173 (100.0%)		359 (100.0%)	
	n	%	n	%	n	%
PP	104	55.9	81	46.8	185	51.5
<PP	82	44.1	92	53.2	174	48.5

Abbreviations: PP, Per Protocol; <PP, Less Than Per Protocol

Table 4

Comparison of PP RT and < PP RT Patient Groups

	<u>Per Protocol</u> (n=216)		<u>< Per Protocol</u> (n=200)		p-value [*]
	n	%	n	%	
Age					
Median		63		60	0.25
Min-Max		33-84		35-80	
Gender					
Male	120	56	115	58	0.69
Female	96	44	85	43	
KPS					
60-80	84	39	68	34	0.30
90-100	132	61	132	66	
Location					
Head	185	86	174	87	0.69
Non-Head	31	14	26	13	
Tumor Size					
< 3 cm	89	41	82	41	0.97
≥ 3 cm	127	59	118	59	
T-Stage					
T1/T2	51	24	50	25	0.74
T3/T4	165	76	150	75	
N-Stage					
N0	74	34	66	33	0.79
N1	142	66	134	67	
Surgical Margins					
Positive	89	41	81	41	0.32
Negative	68	31	75	38	
Unknown	59	27	44	22	

	Per Protocol		< Per Protocol		p-value [*]
	(n=216)		(n=200)		
Tumor Differentiation					
Well	34	16	31	16	0.99
Moderate	116	54	107	54	
Poor/Unknown	66	31	62	31	
CA 19-9					
Lewis Antigen Negative	63		59		
<90	104	68	87	62	0.64
90 – <180	7	5	10	7	
≥ 180	13	9	15	11	
Missing	29	19	29	21	

^{*} t-test for continuous comparison; chi-square test for categorical comparison

Table 5

Multivariate Analysis for Overall Survival

Head of Pancreas Patients Only (n=359)

Adjustment Variables	Comparison	Adjusted HR	p-value [†]
Treatment	Gemcitabine vs. 5-FU	0.79 (0.62, 0.99)	0.043
Nodal Involvement	No vs. Yes	1.47 (1.13, 1.91)	0.0036
Tumor Diameter	<3 vs. ≥ 3cm	1.25 (0.98, 1.59)	0.070
Surgical Margin Status	Negative	Ref level	--
	Positive	1.07 (0.82, 1.40)	0.64
	Unknown	0.94 (0.69, 1.27)	0.68
RT QA Score	< PP vs. PP	0.75 (0.60, 0.95)	0.016

Abbreviations: 5-FU, fluorouracil; HR, hazard ratio; C.I., confidence interval

Hazard Ratio (HR) > 1 indicates increased risk of death for the second variable; HR < 1 indicates decreased risk of death for the second variable

[†] p-value from Chi-square test using the Cox proportional hazards model.

Table 6

Correlation Between Occurrence of Failure and Radiotherapy QA Score Occurrence of (First) Failure by RT Compliance (n=416)

	Failure (n=347)		No Failure (n=69)	
	n	%	n	%
Per Protocol	171	49.3	45	65.2
Less Than Per Protocol	176	50.7	24	34.8
p-value (Chi-square)	0.016			

Grade 3+ Acute (≤ 90 days from the end of treatment) Toxicity (n=416)

	RT+5-FU Arm (n=211)			RT+Cemcitabine Arm (n=205)		
	PP** (n=117)	<PP (n=94)	One-sided p-value	PP (n=99)	<PP (n=106)	One-sided p-value
Heme Gr3+4	9%	9%	NS*	55%	64%	0.094
Heme Gr 4	0%	1%	NS	11%	18%	0.076
Non-Heme Gr 3–5	61%	60%	NS	55%	57%	NS
Non-Heme Gr 4+5	7%	4%	NS	6%	12%	0.065

$$*NS = > 0.10$$

**
PP = Per Protocol