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Comparison of conventional and 3-dimensional computed tomography against histopathologic examination in determining pancreatic adenocarcinoma tumor size: Implications for radiation therapy planning

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Abstract

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Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2012.07.004>.

Background and purpose—This study seeks to: (a) quantify radiologic-pathologic discrepancy for pancreatic adenocarcinoma by comparing tumor size on conventional computed tomography (C-CT) and 3-dimensional CT (3D-CT) to corresponding pathologic specimens; and (b) to identify clinico-pathologic characteristics predictive of radiologic-pathologic discrepancy to assist radiotherapy planning.

Materials and methods—Sixty-three patients with pancreatic adenocarcinoma and preoperative C-CT and volume-rendered 3D-CT imaging within 6 weeks of resection were identified. Maximum tumor diameter (MTD) was measured on pathology, C-CT, and 3D-CT and compared for each patient as well as among different clinico-pathologic subgroups.

Results—There was a trend toward C-CT underestimation of MTD compared to final pathology ($p = 0.08$), but no significant difference between 3D-CT MTD and pathology ($p = 0.54$). Pathologic tumor size was significantly underestimated by C-CT in patients with larger pathologic tumor size (>3.0 cm, $p = 0.0001$), smaller tumor size on C-CT (<3.0 cm, $p = 0.003$), higher CA19-9 (>90 U/mL, $p = 0.008$), and location in the pancreatic head ($p = 0.015$). A model for predicting pathologic MTD using C-CT MTD and CA19-9 level was generated.

Conclusions—3D-CT may allow for more accurate contouring of pancreatic tumors than C-CT. Patients with the above clinico-pathologic characteristics may require expanded margins relative to tumor size estimates on C-CT during radiotherapy planning.

Keywords

Pancreatic cancer; Resectable; Radiation treatment planning; 3D-CT; SBRT

The optimal treatment for locally advanced pancreatic cancer is controversial, but may include chemotherapy alone, chemoradiation, or induction chemotherapy followed by chemoradiation [1]. Modern radiotherapy (RT) for pancreatic adenocarcinoma relies on computed tomography (CT) to delineate target tumor volumes. In conventionally fractionated RT, gross tumor volume (GTV) on CT is expanded to cover non-visualized disease (clinical target volume, CTV) and then further enlarged to accommodate breathing and set-up error (planning target volume, PTV). Presently, limited data exist to define optimal margin size, although guidelines have been suggested by expert committees for CTV [2] and PTV [3].

Stereotactic body radiation therapy (SBRT), which delivers high dose in 1–5 fractions, achieves local control rates above 80% [4], superior to conventional CRT rates (40–50%) [5,6]. High dose per fraction, however, can damage adjacent normal structures, such as duodenum and stomach. One study described a marked increase in pain, nausea and worsened performance status after SBRT in as little as 14 days [7]. Even with GTV-PTV margins reduced to 2–3 mm, one-year grade 2–4 toxicity rates approach 28% [8]. Unsurprisingly, volume of duodenum irradiated correlates strongly with toxicity [9]. However, due to rapid dose drop-off beyond the PTV, decreasing dose to the duodenum and other organs by shrinking margins may increase chances of missing radiologically-occult disease, leading to locoregional recurrence.

Our goal in this study is to assess the amount of pathologically-evident disease not visualized on CT in order to more accurately determine the margin expansion necessary to cover radiologically-occult disease. A previous study showed that maximum tumor diameter (MTD) on gross pathology was a median of 7.0 mm larger than MTD on CT with coronal and sagittal reformats [10]. These differences translate into considerable discrepancy in tumor volumes during contouring. Recently, technology has been adopted at our institution allowing volumetric reconstruction of multi-detector row CT data in 3-dimensions (3D-CT), which promises better visualization of complex pancreatic anatomy [11].

Here we examine whether C-CT or 3D-CT better predicts pancreatic tumor size when compared to the gold standard of pathologic measurement following resection. We also examine whether any clinico-pathologic characteristics are associated with degree of radiologic-pathologic discrepancy. Lastly, we construct a standard curve to predict pathologic size from CT size and available clinical information in order to optimize RT planning.

Materials and methods

Patient selection

We conducted an IRB-approved retrospective chart review of patients with resected pancreatic adenocarcinoma consecutively treated at Johns Hopkins Hospital (JHH) from 2006 to 2010. Patients were included if they had routine preoperative C-CT and 3D-CT within 6 weeks of surgical resection.

Radiology

2D axial conventional CT (Fig. 1a) and volume rendered 3D-CT (Fig. 1b) were available for all patients. MTD was defined as the largest tumor dimension in any plane. At our institution, conventional CT scans are read by several staff radiologists. 3D-CT scans require special processing and are read only by senior radiologist EKF. A separate report is dictated for each modality.

In our study, MTD was indicated in the original radiology report for both C-CT and 3D-CT for 36 patients. For these patients, measurements on C-CTs were done by staff radiologists while those on 3D-CTs were made by EKF only as is normal procedure. Another 27 patients were missing MTD information from either the C-CT or 3D-CT reports. For these patients, EKF re-read all scans specifically to determine the C-CT and 3D-CT MTDs for this study.

Computed tomography technique

Abdominal CT scans were performed from the lung bases to the inferior pelvis on either a 64 MDCT or Dual Source CT Scanner using dual phase acquisition with the arterial phase at a 30 s delay and the venous phase at a 60 s delay. Scan protocol was typically 120 kVp, 150–200 mAs, and collimation of 0.6 mm. The data were reconstructed at 0.75 mm slice thickness at 0.5-mm intervals. This isotropic dataset was then sent to a free-standing workstation and real-time analysis was performed by experienced radiologists using a combination of axial imaging, multiplanar reconstruction (coronal, sagittal, and oblique

planes), and 3D volume rendering in order to optimally visualize the tumor and attempt to precisely define its borders. The interactive rendering and real-time post processing allows any arbitrary plane to be viewed in order to optimize lesion definition and boundary detection. Both phases of acquisition were analyzed, although the venous phase was usually optimal for boundary detection. Measurements of tumor size were then performed on the isotropic dataset and recorded.

Pathology

Surgically-resected pancreata were dissected fresh using standard methodology as described by Westra [12]. Briefly, after appropriate margins were obtained, pancreata were sectioned at the level of tumor and maximum dimension of grossly appreciable carcinoma was measured. Pathologic MTD, tumor staging, and margin status were obtained from original pathology reports. CA19-9 values were obtained from preoperative clinic visits.

Statistical analysis

Differences in MTD among pathology, C-CT and 3D-CT for all patients and for select subgroups of patients were calculated and evaluated for significance using paired-sample Wilcoxon signed-rank tests. Tumor MTDs were transformed logarithmically to reduce skewness. Variables were linearly regressed against pathologic MTD to assess for significant relationships. MTD of 3.0 cm and CA19-9 value of 90 U/mL were used as cutoffs in predicting for radiologic-pathologic discrepancy because 3.0 cm was the median pathologic tumor size in our study and 90 U/mL was previously shown to have prognostic utility [13]. Stepwise selection based on the AIC criterion [14] was used to select the model that best predicts for pathologic MTD. STATA 11 (Statacorp LP) and R were used to perform the analyses.

Results

Patient characteristics (Table 1)

Sixty three patients with preoperative imaging and subsequent resection for pancreatic adenocarcinoma were identified. Thirty six patients received pancreaticoduodenectomy, 13 received pylorus-sparing pancreaticoduodenectomy, 12 received distal pancreatectomy, and 2 received total pancreatectomy. Fourteen patients underwent neoadjuvant treatment. Mean time elapsed between CT and surgery was 15.8 days (range, 3–34 days). Forty eight patients were seen preoperatively at the pancreatic cancer multidisciplinary clinic [15].

Clinico-pathologic features

All patients had pancreatic adenocarcinoma, 61% involving the pancreatic head. 94% were histologic grade 2–3 and 73% were pT3–pT4. 71% had pathologic nodal involvement. Median and mean preoperative CA19-9 (available for 55 patients) were 108.8 U/mL and 327.5 U/mL, respectively. Negative margins were achieved in 73%. Among margin-positive cases, the uncinate margin was most commonly involved (41%).

Median pathologic, C-CT, and 3D-CT maximum tumor diameter (MTD) were 3.0, 2.8 and 2.9 cm, respectively (Table 2). There was a trend toward C-CT underestimation of MTD

compared to gross pathologic examination ($p = 0.08$). Although the median difference was 0 cm, CT underestimated MTD pathology by a mean of 3.2 mm. On the other hand, 3D-CT MTD was not significantly different from MTD pathology ($p = 0.54$). However, MTD 3D-CT was larger by a median of 2.0 mm than C-CT ($p = 0.05$). A wide range existed in the degree of radiologic–pathologic discrepancy (Fig. S1).

Prediction of radiologic–pathologic discrepancy

We analyzed clinico-pathologic variables which may predict underestimation of MTD by C-CT and 3D-CT (Table 3; Fig. S2a and b). Tumors with pathologic MTD >3.0 cm were underestimated on C-CT by a median of 11.0 mm ($p = 0.0001$) and on 3D-CT by 8.0 mm ($p = 0.0001$) compared to pathology. Tumors with pathologic MTD <3.0 cm were overestimated on C-CT (trend only) by a median of 2.5 mm ($p = 0.08$) and on 3D-CT by 4.2 mm ($p = 0.002$) compared to pathology.

Conversely, tumors with C-CT MTD <3.0 cm were underestimated by a median of 6.5 mm compared with pathology ($p = 0.003$). Similarly, tumors with 3D-CT MTD <3.0 cm were underestimated by 2.0 mm compared to pathology ($p = 0.023$). Tumors with MTD >3.0 cm on C-CT and 3D-CT showed no significant difference from pathology.

Tumors with CA19-9 levels >90 U/mL were underestimated on C-CT by a median of 5.0 mm compared to pathology ($p = 0.008$) while tumors with CA19-9 ≤ 90 U/mL were not ($p = 0.92$). Tumors in the pancreatic head were underestimated by 2.0 mm on C-CT compared to pathology ($p = 0.015$), while tumors located elsewhere in the gland were not ($p = 0.41$). CA19-9 > 90 U/mL, location in the pancreatic head, and T-stage 3–4 did not predict significant underestimation by 3D-CT.

Other variables including neoadjuvant therapy, resection margin involvement, tumor grade, and nodal status did not show significant association with radiologic–pathologic discrepancy.

Regression analysis

Univariate analysis revealed that log-transformed ($\ln$) [MTD Pathology] correlated weakly with $\ln$ [MTD C-CT] ($r = 0.435$; $p < 0.001$) and $\ln$ [MTD 3D-CT] ($r = 0.399$; $p = 0.001$). No significant correlation was observed between $\ln$ [MTD Pathology] and patient sex, age, tumor grade, CA19-9, nodal involvement, T-stage, tumor location, resection margin status, CT-resection time interval, or neoadjuvant therapy.

A multivariate analysis was conducted using the AIC criterion to generate a model that best predicts $\ln$ [MTD pathology] from our array of clinical variables. Using $\ln$ [MTD C-CT] and [CA19-9 >90 U/mL] generated the model with the best fit (below).

MTD Pathology = $e^{[0.51842 + 0.49061 \times \ln(\text{MTD C-CT}) + 0.15982 \times (\text{CA19-9} > 90)]}$, where (MTD C-CT) is in centimeters and (CA19-9 >90) equals 1 if CA 19-9 level is >90 U/mL and 0 if ≤ 90 U/mL.

Our model predicts that tumors which appear small on C-CT (<3–4 cm) and have CA19-9 >90 U/mL tend to be larger on pathology. However, the correlation between MTD Pathology and MTD CT is poor with a large degree of variation. Our adjusted $R^2 = 0.17$, shows our model only accounts for a small amount of the variation (Fig. 2).

Discussion

In our cohort of patients with resected pancreatic adenocarcinoma, there was a trend toward C-CT underestimation of pathologic MTD by a mean of 3.2 mm ($p = 0.08$). These results likely derive from poor visualization of infiltrative tumor extension by C-CT and suggest that reliance on C-CT imaging alone can lead to contour margins which may miss a significant amount of pathologically-evident disease. Measuring MTD by C-CT becomes especially difficult along the longitudinal dimension, particularly if thicker slices (>2 mm) are used.

Reformatting of CT data allows display of cross-sectional images in the coronal and sagittal plane in addition to the traditional axial plane, thus facilitating improved visualization of tumor dimensions. However, a study by Arvold et al. [10] found that even measurement on these reformatted images tended to underestimate MTD by a median of 7.0 mm. One drawback of reformatted images is that they are still 2D cross-sections without any depth or volume.

Recently, software used at our institution has allowed for “3D-CT” volumetric rendering of the abdominal cavity, allowing for images to be displayed in virtually any plane while greatly improving depth perception. A study using this technology demonstrated superior discrimination of resectability and vascular invasion for tumors located in the anatomically-complex region of the pancreatic head [16].

3D-CT also appears to allow more accurate approximation of pathologic tumor size, as supported by our finding that 3D-CT MTD was not significantly different from pathologic MTD ($p = 0.54$). The ability to perceive tumors in volumetrically-rendered 3D space may have allowed our radiologist to better define tumor size. This may partially explain the lack of a statistical difference between pathologic and 3D-CT MTD in our study, while a 7.0-mm radiologic underestimation was found by Arvold et al. In addition, there were slight differences in patient populations between our studies (Table S1).

In our study, C-CT underestimated pathologic MTD by a mean of 3.2 mm, approximately the size of typical margins added to GTV when constructing the PTV in SBRT cases [8]. However, the amount by which C-CT underestimated MTD varied greatly among patients. Being able to predict when C-CT will significantly underestimate tumor size allows expansion of margins in patients most likely to benefit.

We found that larger pathologic MTD (>3.0 cm) and higher preoperative CA19-9 (>90 U/mL) predict the underestimation of MTD by C-CT. We hypothesize that larger tumors and those associated with higher CA19-9 are more advanced and infiltrative tumors, the full extent of which are less likely to be visible radiologically. These results agree with Furukawa et al. who demonstrated increased radiologic–pathologic discrepancy for larger

tumors [17], Higher CA19-9 levels are also associated with more aggressive tumors more likely to be unresectable or to yield margin-positive resections [18].

Pancreatic head location was additionally associated with C-CT underestimation of pathologic MTD. This may be due to imaging difficulties resulting from complex regional anatomy [19]. In fact, Arvold et al. found that pancreatic head location increased risk of missing a tumor entirely on initial CT. In contrast, we found 3D-CT did not underestimate pathologic MTD in pancreatic head lesions, demonstrating its utility in these patients.

Similarly to Arvold et al. we found that tumors appearing small (< 3.0 cm) on C-CT and 3D-CT were often markedly larger on pathology. This underestimation disappeared for tumors appearing larger (>3.0 cm) on CT and 3D-CT. Therefore, clinicians should consider adding larger margins to tumors < 3.0 cm.

Administration of neoadjuvant therapy did not cause a significant difference between tumor size on preoperative imaging and postoperative pathologic specimen. This is likely explained by the fact that the majority of patients received only experimental neoadjuvant vaccine which was not expected to produce any downstaging within the time frame of our study.

Herein we attempted to create a model to predict MTD pathology from variables available to clinicians at time of treatment planning. We first sought to identify variables which correlated with MTD pathology. Univariate analysis revealed that log-transformed pathologic MTD correlated poorly with C-CT MTD ($r = 0.435$, $p < 0.001$) and 3D-CT MTD ($r = 0.399$, $p = 0.001$). Furukawa and Aoki have reported similarly poor correlations with $r = 0.67$ ($p < 0.01$) and $r = 0.65$ ($p < 0.001$) between MTD on C-CT and pathology for 26 and 35 patients with pancreatic adenocarcinoma, respectively [17,20]. A model using only reformatted C-CT MTD to predict pathologic MTD by Arvold et al. resulted in a large standard error of prediction of 11.1 mm.

We attempted to include additional variables besides C-CT MTD to improve the fit of the model. Multivariate analyses based on the AIC criterion showed that C-CT MTD and CA19-9 >90 U/mL created the model which best predicts pathologic MTD. Our model predicts that tumors appearing small on CT and with CA19-9 >90 U/mL will appear larger on pathology. Yet, our model accounted for only a small proportion of the variability in determining pathologic tumor size (adjusted $R^2 = 0.17$).

A fundamental issue likely contributing to the poor correlation observed across all studies is lack of reproducibility in radiologic and pathologic tumor measurement. First, inflammation and fibrosis, which often accompany carcinoma, make it difficult to distinguish true tumor extent [21]. Also, the thickness at which a tumor is sectioned and how tightly the sample is held when measured can both affect reported diameter. Furthermore, we obtained tumor measurements from surgical pathology and radiology reports, where determination of size is usually secondary to examination of margins and resectability, possibly lowering the precision of such measurements. We also note that 27% of our patients had microscopic disease at the resection margins (R1). This indicates that the true extent of these tumors may have been underestimated by gross pathology. However, the amount of disease outside the

margin is likely small and we did not find any significant difference in the degree of radiologic-pathologic discrepancy for patients with R1 versus R0 resections (Table 3).

Conclusions

Our study reveals that volumetrically-rendered 3D-CT appears to more accurately represent pathologic pancreatic tumor size than C-CT. In addition, it suggests that *larger* pathologic size, *smaller* appearance on C-CT, *higher* CA19-9, and pancreatic head location are statistically significant risk factors for C-CT underestimation of pathologic tumor size. For patients with these characteristics, expanded CTV margins may help to cover pathologically-evident disease not visualized by C-CT, while smaller margins may be justified for patients lacking these features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

A pancreatic adenocarcinoma from our series has a maximum tumor diameter (MTD) on (a) axial conventional computed tomography of 4.93 cm, while (b) coronal reconstruction on volume rendered 3-dimensional computed tomography reveals a greater MTD of 6.03 cm.

Fig. 2.

Our model for predicting pathologic MTD (solid line) is plotted against actual pathologic MTD and C-CT MTD of our patients (dots). Tumors and predictive model are grouped by CA19-9 level >90 U/mL or ≤90 U/mL. Dashed line represents 1:1 correlation. *MTD*, maximum tumor diameter; *C-CT*, conventional CT; *Path*, pathology.

Table 1Patient characteristics ($n = 63$).

<i>Clinical features</i>	
Average age at surgery	63.9 Years (range 45–87) (median 64)
Date of surgery	2006–2010
Sex	33 females (52%), 30 males (48%)
<i>Prior treatment</i>	
Any preoperative therapy	14 (22%)
Preoperative vaccine (no chemo/radiation)	7 (11%)
Preoperative chemotherapy only	2 (3%)
Preoperative chemoradiation	5 (7.6%)
<i>Pre-OP evaluation</i>	
Seen first at multi-disciplinary clinic	48 (76%)
CA19-9* levels available	55 (87%)
Conventional CT [†] evaluation	63 (100%)
3D-CT [‡] evaluation	63 (100%)
Mean days between CT and Surgery	15.8 days (Range 3–34 days)
<i>Surgery type</i>	
Distal pancreatectomy	12
Pancreaticoduodenectomy	36
Pylorus sparing pancreaticoduodenectomy	13
Total pancreatectomy	2
<i>Pathologic features</i>	
Adenocarcinoma	63 (100%)
<i>Tumor location</i>	
Pancreatic head	39 (62%)
Uncinate process	4 (6.3%)
Body	6 (9.5%)
Tail	7 (11%)
Head	6 (9.5%)
Head/duodenum	1 (1.6%)
<i>CA19-9</i>	
Mean CA19-9	327.5 U/mL (95% CI = 134.8U/mL)
Median CA19-9	108.8 U/mL
CA19-9 > 90U/mL	31 (56%)
<i>Tumor grade</i>	
Grade 1	4 (6.3%)
Grade 2	32 (51%)
Grade 3	27 (43%)
<i>Tumor T stage</i>	
T1	2 (3.2%)
T2	14 (22%)

T3	43 (68%)
T4	3 (4.8%)
Unknown	1 (1.6%)
<i>Nodal stage</i>	
N0	18 (29%)
N1	45 (71%)
<i>Resection margin</i>	
R0 resection	46 (73%)
R1 resection	17 (27%)
<i>Involved margins</i>	
Uncinate margin	7 (41% of R1 resections)
Superior mesenteric artery margin	3 (18%)
Superior mesenteric vein margin	2 (12%)
Proximal	3 (18%)
Splenic artery	1 (5.9%)
Celiac trunk	1 (5.9%)

* Carbohydrate antigen 19–9.

[†] Computed tomography (CT).

[‡] 3-Dimensional computed tomography.

Table 2

Mean and median maximum tumor diameter for all patients on pathology, conventional CT, and 3D-CT.

	Mean (cm)	Standard deviation	95% CI (cm)	Median (cm)	P value
MTD * Pathology	3.13	1.11	2.86–3.41	3.00	–
MTD CCT [†]	2.81	0.85	2.60–3.03	2.80	–
MTD 3DCT [‡]	3.04	0.91	2.81–3.27	2.90	–
Path-CCT [§]	0.32	1.08	0.49–0.59	0.00	0.078
Path-3DCT	0.09	1.17	–0.20–0.38	0.00	0.54
3DCT-CCT [¶]	0.23	0.79	0.03–0.43	0.20	0.05

* Maximum tumor diameter.

[†] Conventional computed tomography.

[‡] 3-Dimensional computed tomography.

[§] Arithmetic difference between MTD pathology and MTD CCT.

^{||} Arithmetic difference between MTD pathology and MTD 3DCT.

[¶] Arithmetic difference between MTD 3DCT and MTD conventional CT.

Table 3

Evaluation for significant differences between pathologic and radiologic MTD* among subgroups of patients. Numbers represent median arithmetic difference in MTD (in cm) between the two modalities. A positive number indicates that pathologic MTD was greater than radiologic MTD. The Wilcoxon signed-rank test was used to evaluate for significance.

Patient subgroup	Pathologic MTD – CCT (cm)		Pathologic MTD – 3DCT (cm)	
	Median	P value	Median	P value
No previous treatment	0.10	0.13	0.00	0.61
Previous treatment	0.00	0.33	0.05	0.75
Pathologic MTD ≤ 3.0 cm	−0.25	0.08	−0.42	0.002
Pathologic MTD > 3.0 cm	1.10	0.0001	0.80	0.0001
R0 Resection	0.00	0.20	0.00	0.98
R1 Resection	0.30	0.26	0.30	0.28
C-CT† MTD ≤ 3.0 cm	0.65	0.003		
C-CT MTD > 3.0 cm	−0.1	0.11		
3D-CT MTD ≤ 3 cm†‡			0.2	0.023
3D-CT MTD > 3 cm			−0.3	0.081
CA19-9§ 90U/mL	0.00	0.92	0.00	0.93
CA19-9 > 90 U/mL	0.50	0.008	−0.10	0.45
Grade 1 or Grade 2	0.00	0.30	0.00	1
Grade 3	0.20	0.16	0.20	0.43
T stage 1 or 2	0.05	0.82	0.10	0.72
T stage 3 or 4	0.05	0.055	0.00	0.44
N stage 0	0.35	0.21	−0.15	0.9
N stage 1	0.00	0.20	0.10	0.37
Tumor in pancreatic head	0.20	0.015	0.05	0.18
Tumor not in head	−0.10	0.41	0.00	0.46

* Maximum tumor diameter.

† Conventional computed tomography.

‡ 3-Dimensional computed tomography.

§ Carbohydrate antigen 19-9.