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REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

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DOI: 10.5603/RPOR.a2022.0045

Article type: Research paper

Published online: 2022-03-30

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Recurrence patterns of pancreatic cancer treated with adjuvant intensity modulated radiotherapy

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Abstract

Background: The aim of this study was to investigate the recurrence patterns in pancreatic cancer patients treated with adjuvant intensity modulated radiotherapy (IMRT) and to correlate the sites of locoregional recurrence with radiotherapy target volumes.

Materials and methods: Thirty-eight patients who had undergone resection and adjuvant chemoradiation for pancreatic cancer were evaluated. Radiotherapy (RT) was started after 1–3 cycles of adjuvant chemotherapy (CHT). Clinical target volume (CTV) was contoured according to the RTOG guideline. All patients were treated with IMRT with a dose of 45–50.4 Gy. Computerized tomography (CT) images at the time of recurrence were correlated with radiotherapy plans. Locoregional recurrences were classified as in-field, out-field and marginal.

Results: Median overall survival (OS) was 19 months. One- and 2-year OS rates were 73.6% and 37.1%, respectively. Locoregional recurrence and distant metastases were observed in 11 (28.9%) and 23 (60.5%) patients, respectively. For the 11 locoregional recurrences, 7 were in-field, 1 was marginal, and 3 were out-of-field. One patient had isolated local, 2 patients had

isolated regional and 15 (57.6%) patients had only distant failures. The first presentations of failures were mostly distant (58%). On multivariate analysis, tumor size ≥ 3 cm ($p = 0.011$) and positive vascular invasion ($p = 0.014$) predicted for worse OS rate.

Conclusions: The majority of locoregional recurrences were in the radiation field among pancreatic cancer patients treated with postoperative IMRT. However, failures were predominantly distant, and improvement of systemic control may be of particular interest.

Key words: pancreatic cancer; adjuvant chemoradiotherapy; intensity-modulated radiotherapy; recurrence

Introduction

Pancreatic carcinoma is the 7th leading cause of cancer related deaths worldwide [1]. Surgical resection is a potentially curative treatment for this devastating disease. However, only 20% of patients are candidates for surgery at presentation. Most patients develop distant metastases within two years and high rates of local recurrences have been reported after the operation [2]. Therefore, efforts have been made to achieve better treatment outcomes in the adjuvant setting, both with chemotherapy (CHT) and radiotherapy (RT).

The first randomized studies showed better outcomes with chemoradiotherapy (C-RT) [3, 4], despite the fact that the European studies in the nineties supported the use of CHT alone [5, 6]. A significant survival benefit with the use of adjuvant gemcitabine monotherapy compared with surgery alone has been shown in the CONKO-001 trial. Then, better treatment outcomes have been noted with multiagent chemotherapy combinations, such as gemcitabine plus capecitabine or FOLFIRINOX [7, 8]. Locoregional control may become more important with increasing survival by using newer CHT combinations. However, the role of adjuvant RT in resectable pancreatic cancer remains controversial. The serious design flaws of the ESPAC-1 trial, outdated RT techniques used in randomized trials limit the interpretation of the results. Intergroup Trial-RTOG 97-04 is the first trial to use three-dimensional (3-D) conformal RT techniques in combination with CHT in the adjuvant setting [9]. This study showed that patients who were not treated per study protocol had a significantly worse outcome [10]. Also, the data from prospective trials supported that C-RT was not deleterious. In the analysis of the National Cancer Database (NCDB), the survival benefit of C-RT has been noted [11]. The significantly lower rate of local recurrence alone at first progression with C-RT has been shown in a randomized GERCOR phase II study [12].

Last two decades, there have been significant improvements in RT technology such as the use of four-dimensional (4-D) computerized tomography (CT) simulation and Intensity-modulated radiation therapy (IMRT). IMRT has been shown to reduce radiation dose to critical dose-limiting structures and enable better dose distributions that improve toxicity profiles in pancreatic cancer when compared with 3-D conformal RT [13]. In 2009, RTOG 0848 was initiated to investigate the addition of erlotinib to gemcitabine as adjuvant systemic therapy and the use of RT for patients who did not progress after 5 months of systemic therapy. Quality control reviews for each patient randomized to receive radiation were required in this trial [14]. The results of this trial would display the contribution of IMRT in the adjuvant protocol. RT volume contouring and quality assurance (QA) are very important in order to improve locoregional control. Knowledge of locoregional recurrence sites leads to modifications in target volume definition, delivery technique, or dose escalation.

The aim of this study is to investigate the recurrence patterns and correlate the sites of locoregional recurrence with previously treated radiotherapy fields among pancreatic cancer patients treated with IMRT in accordance with RTOG protocol.

Materials and methods

We reviewed the medical records of patients treated with IMRT for resectable pancreatic adenocarcinoma in our department. Between 2010 and 2015, there were 38 patients available for assessment who had undergone postoperative RT for pancreatic carcinoma. The study was approved by our institutional review board (approval number: 21.02.2020/30333). All patients had signed informed consent according to institutional guidelines.

The median age was 58 (30–73) years old, and 25 (65.8%) of the patients were male. All patients were histologically confirmed with pancreaticoduodenectomy. Staging was made according to AJCC 7th. Tumor diameter was median 3.5 (1.0–6.8) cm. The majority of patients (71.1%) had positive lymph nodes. Median 16 (2–42) lymph nodes were dissected and median 2 (0-12) of them were pathologically involved. Negative surgical margins were achieved in 14 (37%) patients. Sixteen patients had positive surgical margins, whereas 8 had a close positive margins (< 2 mm). Patients' and tumor characteristics are shown in Table 1.

All patients received one to three cycles of adjuvant gemcitabine monotherapy (1000 mg/m² weekly for three of every four weeks). Prior to beginning C-RT, all patients underwent formal restaging with CT scans. After the exclusion of distant or locoregional failure, RT was

initiated with concurrent infusional 5-FU (250 mg/m² daily) or capecitabine (750–825 mg/m², divided in twice-daily doses and given Monday through Friday with the radiation treatment). After completion of C-RT, maintenance of single-agent gemcitabine (1000 mg/m² weekly for three of every four weeks) proceeded for a total of 6 months.

RT was started median 89 (47-138) days after surgery. Patients were treated in a supine position with the wing board immobilization. A CT scan in treatment position was obtained on a GE LightSpeed 16-slice CT simulator (GE Medical Systems, Milwaukee, Wisconsin). Planning CT was performed from the trachea bifurcation to the 5th lumbar vertebra with 3 mm intervals. The images were sent to Velocity Contouring Station version 2.8 (Velocity Medical Solutions, Atlanta, GA). Tumor bed was defined and contoured with the fusion of preoperative imaging with planning CT. Clinical target volume (CTV) was contoured according to the RTOG guideline for tumor bed and nodal areas [15]. Planning target volume (PTV) was generated with a 1cm margin in all directions to CTV.

For all plans, the structures contoured in the Velocity Contouring Station were transferred to the Eclipse version 8.6 treatment planning system (Varian Medical Systems, Palo Alto, USA). Varian Clinac DHX linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) with 6–15 MV photon energies was used. RT plans were made with the sliding window IMRT technique. The Isocenter was determined as the midpoint of the PTV volume for all plans. Anisotropic Analytical Algorithm (AAA) photon dose calculation algorithm was used and the maximum dose rate was defined as 300 MU/min. The dose calculation grid was 2.5 mm. 45 Gy was prescribed in 18 patients. In 20 patients who had positive surgical margins, 5.4 Gy boost dose was added to the tumor bed. During the treatment, the motion management system was not used. Target localization was performed based on the bone and the soft tissue matching using kV-CBCT scans before each treatment.

After completion of chemoradiotherapy, patients were seen every 3 months for 2 years and every 6 months for 5 years. History, physical examination and a complete blood count, serum chemistry were obtained on each follow-up visit. CT scans of the chest and abdomen were obtained every 6 months or when indicated.

Locoregional recurrences were defined with CT imaging without histologic confirmation. All radiological imaging examinations of patients with locoregional recurrence were evaluated from the beginning of diagnosis. CT imaging scans at the time of recurrence were matched with radiotherapy planning CT. The volume of the recurrent tumors was contoured on the planning CT. The local and regional recurrences were classified as in-field ($\geq 95\%$ of recurrent tumor was within the 95% isodose line), marginal (20–94% of recurrent tumor was

within the 95% isodose line), or out-of-field (< 20% of recurrent tumor was within the 95% isodose line) according to 45Gy isodose-line. Toxicities were graded using the NCI Common Toxicity Criteria v4.0. Overall survival (OS) rate was defined as the time from surgery to death or last follow-up. Progression free survival (PFS) and locoregional recurrence free survival (LRFS) were defined as the time from the surgery to an event or death and to a locoregional recurrence or last follow-up, respectively. Kaplan-Meier curves were used for survival analysis. Survival time between groups was compared with the Log-Rank test. The effect of variables on survival times was evaluated with Cox- Regression Analysis. All analyses were performed on SPSS v20 and $p < 0.05$ values were accepted as statistically significant.

Results

Median follow up time for patients was 18 (5-59) months. Locoregional recurrence and distant metastases were developed in 11 (28.9%) and 23 (60.5%) patients, respectively. One (3.8%) patient had isolated local, 2 (7.6%) patients had isolated regional and 15 (57.6%) patients had only distant failures (Fig. 1). Median locoregional recurrence free and metastasis free survival were 13 and 11 months, respectively. For the 11 locoregional recurrences, 7 were in-field, 1 was marginal, and 3 were out-of-field (Fig. 2). The first presentation of failure was distant in 15, locoregional in 6 and synchronized in 5 patients. Metastases were seen in the liver (43.4%), lung (17.3%) and peritoneum (13%). Both liver and lung metastases were observed in 4 (17.3%) and peritoneal and bone metastases in 2 (8.7%) patients. Thirty-three patients died and 5 were still alive at the time of our review. Median OS was 19 months. One-, 2- and 3-year OS rates were 73.6%, 37.1% and 24.7%, respectively. Median PFS was 13 months. One-, 2- and 3-year PFS rates were 55.5%, 27.7% and 27.7%, respectively.

When we evaluated prognostic factors for overall survival; patients who were 60 or older had shorter survival rates than younger ones ($p = 0.013$). Patients who had negative surgical margins had significantly higher survival rates than those who had positive surgical margins ($p = 0.023$). Patients whose tumor size was equal or larger than 3cm had shorter survival rates than those with smaller tumor sizes ($p = 0.030$). Also patients who had positive microscopic vascular invasion had shorter survival rates than who had negative one ($p: 0.041$). For PFS, tumor size ≥ 3 cm ($p = 0.03$) and close/positive surgical margin ($p = 0.03$) were found to be negative prognostic factors (Tab. 2).

Multivariate analysis showed that tumor size ≥ 3 cm [hazard ratio (HR): 4.86, confidence interval (CI): 1.44–16.31, $p = 0.011$] and microscopic vascular invasion (HR: 5.23, CI: 1.40–19.61, $p = 0.014$) were associated with worse survival. The OS rate was lower in patients aged 60 years or older compared to patients younger than 60 years old, but the difference was not statistically significant ($p = 0.097$). The surgical margin status was not a statistically significant prognostic factor ($p = 0.63$). No significant prognostic factor was identified to affect both PFS and LRFS rates in the Cox regression analysis. It should be noted that multivariate analysis is limited due to the small sample size.

In general, RT was well tolerated. RT was administered in median 36 (17–48) days. No correlation was found between treatment time and PFS ($p: 0.879$) and OS ($p = 0.740$). Grad 1-2 nausea and abdominal discomfort were observed in 6 (16%) and 4 (11%) patients, respectively. Two patients were unable to complete RT (21.6–27 Gy). One of them had grade 3 gastrointestinal and hematologic toxicity. In this patient's serum chemistry and diagnostic evaluation, peritonitis carcinomatosa and infection were detected. Sole chemotherapy was continued after the recovery. Another patient had psychiatric problems and did not want to continue radiotherapy.

Discussion

Surgery is the standard of care in patients with resectable pancreatic adenocarcinoma. The predominant failure pattern of pancreatic cancer after curative therapy is distant metastases that tend to occur within two years. At follow-ups, locoregional relapses were also reported at significant rates and approximately one third of patients die due to local disease [16]. Local failure can affect patients' quality of life (QoL) with intestinal/bile duct obstruction, bleeding, and pain. However, high distant relapse rates overshadow the importance of local control. Therefore, the main aim after curative surgery is to control both local and distant recurrence in order to prolong survival and improve patients' QoL.

In the nineties, two trials supported the administration of CHT alone. The results of the ESPAC-1 Trial showed that the survival rate was better with CHT but worse with the C-RT (5). In the German CONKO-001 trial, modest improvement in survival with 6-month adjuvant gemcitabine was observed among patients with macroscopic complete removal of pancreatic cancer (22.8 months versus 20.2 months) [6]. Two European studies, subsequently supported the use of chemotherapy. In the ESPAC-3 trial median survival was 23 months with 5-FU/Leucovorin and 23.6 months with gemcitabine, without significant difference [17].

Afterward, in the ESPAC-4 Study median survival was 28 and 25.5 months with gemcitabine/capecitabine and gemcitabine alone, respectively [7]. Recently, the randomized study of Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group showed significant OS benefit (54.4 months) with FOLFIRINOX despite the higher side effect rates [8]. As more effective systemic agents have been used and distant disease has been controlled, local control becomes more important. The GERCOR trial of postoperative gemcitabine versus gemcitabine-based chemoradiotherapy showed that the rate of local recurrence alone (11 vs. 24%) and the simultaneous local and distant progression (13 vs. 20%) at first progression was lower in the chemoradiotherapy group [12]. However, the randomized trials and meta-analyses have failed to show a survival benefit from RT [18]. The limitations of trials, such as the design flaws of the studies, older 2-D RT techniques, split course fractionation schedules, and wide range of doses used, pose difficulties in drawing certain conclusions about the efficacy of C-RT.

Today, more effective radiation therapy can be performed with developing RT techniques. RTOG 9704 is the first randomized trial that used a 3-D conformal RT technique in the adjuvant setting of resected pancreatic carcinoma [9]. Results of this milestone study showed that survival was the same as CHT trials (median 20.5 months). Although distant metastases were still a common problem (73%), the incidence of local recurrence was almost half (28%) of the other studies. Also in the secondary analysis of this study, the inferior survival rate was shown in patients who had not been treated per protocol radiotherapy, which showed the importance of QA and education of radiation oncologists [10]. Recent advances in RT technology, such as IMRT, 4-D CT simulation, allows better protection of normal dose-limiting tissues and more homogeneous dose coverage in the tumor. In the IMRT series, the incidence of normal tissue toxicities has been observed less when compared with 3-D conformal RT. Yovino et al. indicated that there was much lower grade 3–4 nausea/vomiting (0% vs. 11%) and diarrhea (3% vs. 18%) with IMRT compared to RTOG 9704 study using 3-D conformal RT [19]. Abelson et al. concluded that IMRT was well tolerated in the adjuvant setting of operable pancreatic cancer and noted only 9% acute toxicity with IMRT [20]. A systematic review that analyzed 13 studies with IMRT and 7 with 3-D conformal RT came to the conclusion that both modalities had similar oncologic outcomes whereas treatment toxicities were markedly reduced with IMRT [13]. In our study, RT was well tolerated and only one patient had grade 3 treatment related toxicity.

An individual pancreatic cancer patient's prognosis generally depends on the extent of the tumor or nodal spread. Two large data, which confirmed higher survival rates with C-RT,

showed that patients with larger tumor size, positive lymph nodes, and positive margins had worse outcomes [21, 22]. In the present study, tumor size (≥ 3 cm) and margin status were found to be prognostic factors for both OS and PFS on univariate analysis. Also in RTOG 9704, a 3 cm cut-off value was used for stratification of patients. In the latest version of the AJCC staging system (8th), the importance of tumor size was highlighted. In version 7, “tumor extension beyond the pancreas” was changed to “tumor limited to the pancreas and > 4 cm” for T3 definition [23]. Bigger tumor size and adherence to vascular structures that may lead to a positive margin can increase the incidence of relapses. Former randomized studies included patients with both R0 and R1 resection. Although multiagent chemotherapy improved overall survival in these studies, a positive margin still associated with lower survival rates [7]. Furthermore, there was little consensus on the definition of a negative surgical margin, we observed similar survival rates (17 months vs. 15 months) with a < 2 mm margin and a positive margin in our study group. So, we analyzed them together as a positive or close resection margin.

In a large SEER cohort, dissection of 15 lymph nodes was proposed to ensure adequate pathological staging of pancreatic cancer for better OS definition, according to the International Study Group on Pancreatic Surgery (ISGPS) consensus [24]. In a secondary analysis of RTOG 9704, lymph node parameters, including increased positive lymph node, total node dissected (≤ 15) and the ratio of the positive lymph node to total node dissected ($> 33\%$), were found to be prognostic for OS and DFS [25]. We did not find a correlation with the N stage and survival, but there was a trend for worse OS with 3 or more positive lymph nodes. The importance of other pathologic factors is less clear. In a large systematic review, the impact of vascular invasion (VI) and perineural invasion (PNI) were mentioned, although they found a weak association with survival. They also found lower PNI (37%) and VI (17%) rates, in contrast to our study of more than 85% [26]. In the present study, we noted that VI was associated with worse survival. An ongoing study explores a novel PNI and VI scoring system and correlation of adverse factors with disease free survival (NCT04024358).

Our approach is to suggest adjuvant C-RT based on risk evaluation. There are also publications that support C-RT in all situations. Two institutions that treat high-volume patients with pancreatic carcinoma reported that survival with C-RT improved in all risk groups compared to surgery alone (median survival 21.1 vs. 15.5 months) [27]. The majority of our patients had T3–4 tumors (92%), close/positive resection margins (63%), and positive lymph nodes (71%). Compared to other randomized studies, our study group included more patients with high risk factors. Although having more patients with negative prognostic

factors, we observed lower locoregional relapses compared to favorite randomized trials (29% vs. 28–60%), whereas consistent with RTOG 9704 (28%).

In this study, the most commonly seen site of recurrence was the retroperitoneal tissue which was in the radiation field. This might be due to the high rate of positive retroperitoneal margins. Similarly, in an analysis of local control with IMRT, most of the recurrences were found in the 45 Gy isodose-line for resected pancreatic carcinoma [28]. In-field recurrence is reassuring in terms of the quality of target volume definition while showing the radioresistant clones. Dose escalation to the highest risk regions may have an impact on local control. IMRT facilitates dose escalations, improve the toxicity profiles, and the patients' quality of life. A study with concurrent fixed-dose rate gemcitabine in locally advanced pancreatic cancer showed that dose escalation to 55 Gy could be safely used with IMRT and breath hold techniques [29]. SCALOP-2 trial has recently tested the intensification of radiation dose (50 vs. 60 Gy) with a radiosensitizer nelfinavir in locally advanced pancreatic carcinoma [30]. At this point, it may be reasonable to intensify the dose with stereotactic body radiotherapy (SBRT) in neoadjuvant setting of borderline resectable pancreatic carcinoma to achieve a higher local control and negative surgical margin.

An important limitation of the data reported here is that this is a single-center retrospective study with a small group of patients, which significantly restricts findings. Another limitation is that we could not reach the serum level of the tumor marker CA 19-9 of all patients and analyses were performed without taking this important prognostic factor into account. Regarding the treatment technique; we did not use any motion management strategy during the study period. Lastly, there is no comparison group that receives only CHT after surgery. It may be helpful to understand our institutional results related to the treatment types of all pancreatic cancer patients.

In conclusion; the majority of locoregional recurrences were found to be in the radiation field among pancreatic cancer patients treated with postoperative IMRT. This demonstrates the adequacy of CTV delineation according to RTOG contouring guideline but further research on dose escalation may be required. However, failures were predominantly distant, and improvement of systemic control may be of particular interest.

Conflicts of interest

None declared.

Funding

This publication was prepared without any external source of funding.

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Table 1. Patients and tumor characteristics

	n	%
Gender		
Male	25	66
Female	13	34
Grade		
1	2	5
2	26	69
3	10	26
Location		
Head of pancreas	32	84
Periampullar	6	16
Surgical margin		
Negative	14	37
Close/positive	24	63
T stage		
2	3	8

3	28	74
4	7	18
N stage		
Node negative	11	29
Node positive	27	71
Lymphatic invasion		
No	3	8
Yes	35	92
Vascular invasion		
No	6	16
Yes	32	84
Perineural invasion		
No	0	0
Yes	38	100

Table 2. Univariate analysis of prognostic factors

	N	OS (%)			PFS (%)			LRFS (%)		
		1 year	2 year	P value	1 year	2 year	P value	1 year	2 year	P value
Age										
< 60	22	81.8	49.2	0.013	61.0	35.6	0.203	94.4	68.4	0.180
≥ 60	16	61.9	18.3		45.3	11.3		70.9	60.8	
Gender										
Male	25	75.8	35.4	0.459	67.7	33.8	0.065	95.5	63.6	0.458
Female	13	69.2	38.5		34.2	17.1		63.5	63.5	
Grade										
1	2	100	0	0.536	0	0	0.180	50.0	50.0	0.526
2	26	76.9	41.4		65.2	30.1		90.0	63.5	
3	8	50.0	33.4		45.0	22.5		72.9	72.9	
Tumor size										
< 3 cm	9	87.5	45.0	0.030	77.8	62.2	0.030	88.9	74.1	0.836
≥ 3 cm	29	69.0	34.1		47.9	17.4		83.3	60.6	
Surgical margin										
	14	85.1	68.8	0.023	85.1	47.3	0.030	81.8	63.6	0.712

- +/Close	24	66.7	19.4		37.2	15.9		74.9	65.6	
Vascular invasion	6	100	100	0.041	100	60.0	0.272	100	80.0	0.249
- +	32	68.6	25.2		49.1	22.3		81.1	57.5	
Positive lymph node										
< 3	20	80.0	47.4	0.069	52.0	34.7	0.813	89.7	83.7	0.068
≥ 3	18	66.7	25.9		59.7	17.0		77.6	39.4	

OS — overall Survival; PFS — progression free survival; LRFS — locoregional recurrence free survival

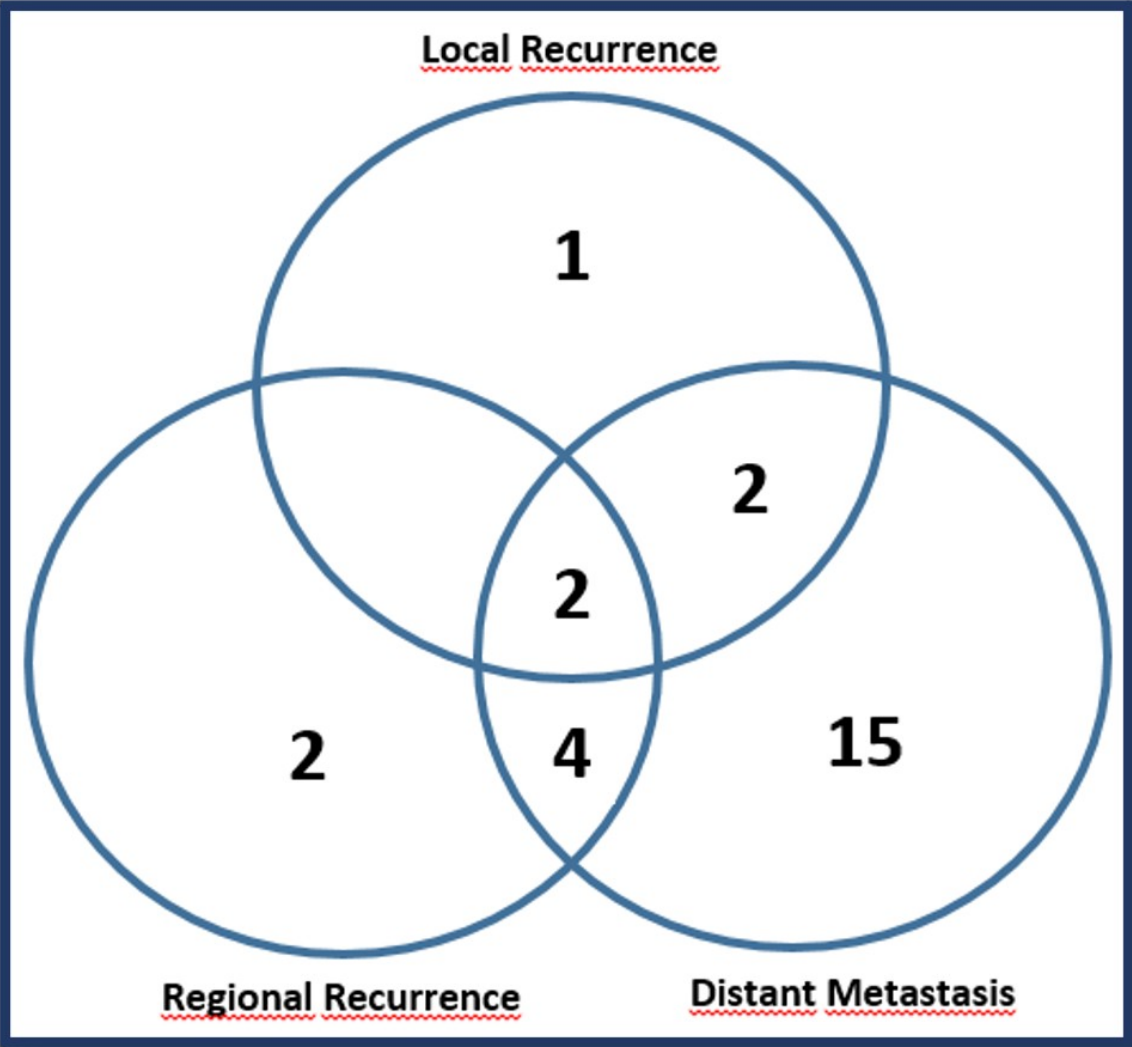


Figure 2. In-field recurrent tumor in sagittal and coronal fusion view of radiation therapy (RT) planning computed tomography (CT) and the control CT

