

## Mide Kanserli Hastalarda Radyoterapi Hacimlerine Göre Lokal Bölgesel Yineleme Alanlarının Tanımlanması

### Failure Sites with respect to Radiotherapy Volumes in Gastric Cancer Patients

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#### ÖZET

**GİRİŞ ve AMAÇ:**Bu çalışmanın primer amacı, küratif cerrahi ve adjuvan kemoradyoterapi (KRT) uygulanan mide adenokarsinomlu hastaların lokal yineleme bölgelerini radyoterapi planları ile birleştirilerek tanımlamaktır. İkincil amaç ise sağkalım sonuçlarını sunmaktır.

**YÖNTEM ve GEREÇLER:**İki merkezde küratif rezeksiyon yapılan ve adjuvan KRT alan 62 erişkin mide adenokarsinomlu hasta retrospektif olarak incelendi. Radyoterapi 25-28 fraksiyonlarda 4500-5040 cGy olarak uygulandı. Takipte, nüksün tariflendiği bilgisayarlı tomografi görüntüleri RT planlama sistemine aktarıldı ve RT izodoz eğrilerine göre nüks bölgesi tanımlandı.

**BULGULAR:**Ortanca takip süresi 18 aydı, 22 hastanın (%35) hastalığı tekrarladı. Beş hastada izole lokal-bölgesel başarısızlık (3 nodal, 2 lokal nüks) görüldü. Bu nükslerin üçü RT alanında, biri marjinal nüks, kalan biri de RT alanı dışında idi. İki nodal nüks, %95 ve %100 izodoz eğrisi içinde kalırken, diğer nodal nüks ise reçete edilen dozun %20'sini oluşturduğu izodoz hattında idi. Bir lokal nüks, %90 izodoz eğrisi içinde, anastomoz bölgesinde, diğeri ise %50 izodoz eğrisi içinde, peritoneal yüzeydeydi. Üç ve beş yıllık genel sağkalım (GS) sırasıyla %71 ve %55 olarak bulundu. D2 lenf nodu diseksiyonu yapılan hastalarda genel sağ kalım daha yüksek olup farklılık istatistiksel olarak anlamlı düzeyde bulunmadı.

**TARTIŞMA ve SONUÇ:**Lokal nüks bölgesinin tanımlanması RT hedef hacmin belirlenmesinde yol gösterici olabilir. Bunun için daha fazla hasta ile yapılan kontrollü çalışmalara ihtiyaç bulunmaktadır.

**Anahtar Kelimeler:** lokal-bölgesel nüks, gastrik karsinom, kemoradyoterapi

#### ABSTRACT

**INTRODUCTION:**The primary aim of this study is to evaluate and define locoregional recurrence regions individually matching with radiotherapy (RT) plans in gastric adenocarcinoma patients treated with curative surgery and adjuvant chemoradiotherapy (CRT). The secondary aim is to present the survival results.

**METHODS:**62 adult gastric adenocarcinoma patients who underwent curative resection and received adjuvant CRT at two radiation oncology centers were analyzed. The 4500-5040 cGy was delivered in 25-28 fractions. At follow-up, computed tomography, which described recurrence, was transferred to the RT planning system and defined the site of relapse according to RT isodose curves.

**RESULTS:**The median follow up time was 18 months, 22 patients (35%) have been relapsed. Five patients had isolated loco-regional failure. Three of these relapses were in the RT field, one was marginal recurrence and the remaining one was outside the RT field. Two nodal recurrence regions were covered by 95% and 100% isodose lines and the other nodal recurrence region was covered by 20% isodose line with respect to their initial radiotherapy volumes. One local recurrence was in the anastomosis site covered by 90% isodose line and the other was on the peritoneal surface covered by 50% isodose line. The 3 and 5-year overall survival (OS) were 71% and 55% respectively, and were better with D2 lymph node dissection without statistical significance.

**DISCUSSION AND CONCLUSION:**Identification of the local recurrence site may be helpful in determining the RT target volume. For this, controlled studies with more patients are needed.

**Keywords:** loco-regional recurrence, gastric carcinoma, chemoradiotherapy

## INTRODUCTION

Gastric Cancer is the 3rd leading cause of death worldwide accounting for over 782000 deaths in 2018 (1). The mainstay of curative treatment is complete resection with adequate margins and nodal dissection. High incidence of recurrence rate even after optimal surgery has led to the use of adjuvant therapies in an attempt to decrease locoregional and distant relapse. Survival benefit with chemotherapy is well-defined with a meta-analyse (2) mainly confined to or driven by Asian trials (2-5).

Surgical series document that locoregional recurrence occurs in 40-60% of patients, especially in tumor bed, anastomosis site, and regional nodes in stage 2-3 disease. Within this context, radiotherapy (RT) is a good method to increase locoregional control, thus improve outcome (6-8). Another way to overcome the nodal component of locoregional failure is to extend the dissection. Although meta-analyses demonstrated that D2 node dissection can improve survival in patients with resectable gastric carcinoma, the increased incidence of postoperative mortality reduces its benefit (9).

Beginning from the Intergroup 0116 (INT 0116) trial published first in 2001, combination therapies with chemotherapy and radiation (CRT) demonstrated local control and survival advantage in different series both in D1 and D2 dissected subgroups and has become standard adjuvant treatment for gastric adenocarcinomas (10-12).

However, toxicity is a concern in patients treated with CRT (10,13). In the INT 0116 trial, where 4500 cGy of radiation was delivered in 25 fractions to the tumor bed and regional nodes with generous margins in two-dimensional (2D) manner, especially hematologic and gastrointestinal acute side effects were the reason for cessation of treatment in 17% of patients.

Three-Dimensional Conformal Radiotherapy (3D-CRT) and Intensity Modulated Radiotherapy (IMRT) techniques allow further tailoring of the irradiated volume to avoid excessive acute and late toxicity without compromising local control (14). It is highly important to determine characteristics of local failures with respect to RT volumes even in D2 dissected gastric cancer patients to guide for further treatment alternatives. It can give us an idea about the delineation of target volume with modern RT techniques and the need for dose escalation. It is not known that how many local recurrences are within the RT area and whether relapses can be prevented if the RT field can be expanded. In this respect, current study was aimed to analyze recurrence patterns of gastric adenocarcinoma patients and survival rates treated with curative surgery and adjuvant CRT in two different radiation oncology centers in Turkey.

## MATERIAL METHOD

We conducted a retrospective review of 62 adult gastric adenocarcinoma patients who underwent curative resection and received adjuvant CRT at our institutions, between July 2010 and July 2015. Data were assembled using hospital medical records. Following preoperative assessment, a total or subtotal gastrectomy and lymph node dissection was done. Splenectomy was not routinely carried out. Patients were staged using the TNM 7th edition. Adjuvant CRT was offered to all patients irrespective of their age if they had good performance (ECOG 2) with stages 1b through 3. Chemoradiotherapy was initiated 4-6 weeks postoperatively. Chemotherapy agents were either intravenous 5-Fluorouracil and Folinic Acid or oral Capecitabine. The 4500-5040 cGy was delivered in 25-28 fractions to the tumor bed, anastomosis site, duodenal stump, remaining stomach if surgical margins around the primary tumor is less than 5 cm and regional lymph nodes (LNs) according to tumor

localization with 1 to 1.5 cm additional margin either 3D-CRT or IMRT.

Patients were checked weekly by their treating radiation oncologist and medical oncologist for acute toxicity during RT course and then followed up every 3 months for 2 years unless otherwise specified. Follow up consisted of physical examination, complete blood count, liver and kidney function tests, abdominal ultrasonography or computed tomography (CT) scans and upper gastrointestinal endoscopy as clinically indicated. Patients who are lost to follow up and could not manage to finish the planned treatment were excluded from the study. Recurrences were classified as local, regional and distant. Local recurrence was defined as recurrence at tumor bed, anastomosis site, duodenal stump and remaining stomach. Regional recurrence was defined as recurrence at the regional lymph nodes within the radiation portal. Common hepatic, celiac, splenic, hepatoduodenal LNs (except splenic hilar LNs) involved in the irradiated volume were categorized as group 2 LNs, whereas LNs at the posterior plane of the pancreatic head, superior mesenteric vein, or para-aortic LNs between the upper border of the onset of the celiac artery and the lower border of the left renal artery contained in the irradiated volume were categorized as group 3 LNs. Metastasis in liver, lung and other organs accepted as distant relapse. Since conformal RT fields do not encompass whole peritoneal cavity, peritoneal carcinomatosis, independent from the location of this deposits, was scored as distant relapse also. First radiological recurrence and histological (whenever possible) confirmation date and time of death were recorded. Follow up data were analyzed and the site of first recurrence was detected and contoured on diagnostic CT images with consultation of another radiologist for final decision. Thus, isolated local recurrences identified. Then, CT images of locally recurred patients were transferred to radiation planning system and fused with RT planning CT. The landmarks for

fusion were vessels primarily and bones. Recurrent lesion contours were transferred to the planning CT with the help of consultant radiologist. The plan of RT copied to CT where recurrence was detected and the isodose lines encompassing recurrent lesions were obtained. Recurrences encompassing by the 90% isodose line (dose curve in 90% of RT dose) were considered to be in field, 50-90% isodose lines were marginal. If it was not covered by 50%, it was considered out of field.

### *Statistical Analysis*

Statistical analysis was performed using SPSS version 22. Kaplan-Meier survival analysis was used to estimate overall survival (OS). The log rank test was used for comparison of survival curves. We defined OS as the time from surgery to death from any cause. Cox regression was used to identify factors affecting survival. All statistical tests were conducted two-sided and a p-value 0.05 was regarded statistically significant.

## **RESULTS**

From July 2010 to July 2015, 62 curatively resected gastric adenocarcinoma patients who received CRT were identified. Patient and disease characteristics are shown in Table 1. Tumor was placed generally to antrum while pain and weight loss were the most presenting symptoms. R0 resection (97%) and D2 dissection (55%) was obtained predominantly. Apart from two patients with surgical margin positivity, all patients received 4500 cGy RT concomitant with mainly FUFA chemotherapy.

After a median follow up of 18 months (range 5-67 months), 22 patients (35%) had experienced relapse. The 3 and 5-year OS were 71% and 55% respectively. Overall survival rates were found better with D2 dissection without statistical significance (Figures 1). Other prognostic factors affecting survival were

analyzed using Cox regression model. No Table

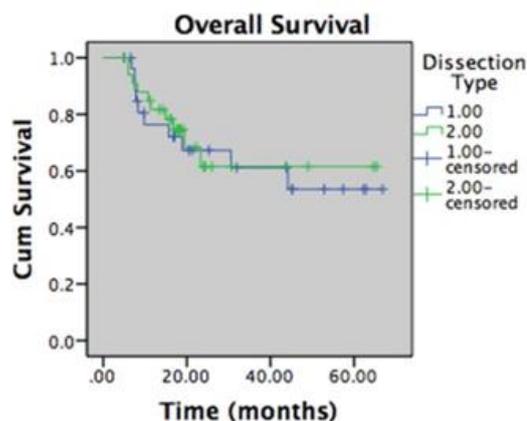
**1. Characteristics of Patients**

Gender	Female	19 (31%)
	Male	43 (69%)
Age	Mean	60(SD:10.2)
	Median	61(34-80)
Tumour Dimension	Mean	3.9cm (SD:2.7)
	Median	3 cm(range:1-13)
Dissected Nodes	Mean	27(SD:14.6)
	Median	25(range:1-75)
Involved Nodes	Mean	5(SD:5.8)
	Median	3(range:0-24)
Dissection Type	D1	28 (45%)
	D2	34 (55%)
T Stage	T1	2 (4%)
	T2	6 (11%)
	T3	22 (34%)
	T4	32 (51%)
N Stage	N0	16(26%)
	N1	13(21%)
	N2	10(16%)
	N3	23(37%)
Stage	Stage1	4(6%)
	Stage2	18(29%)
	Stage3	40(65%)
Margins	Positive	2(3%)
	Negative	60(97%)
Total RT doses	45Gy	60(97%)
	50.4Gy	2(3%)
Chemotherapy	FUFA	52(83%)
	Capesitabine	10(17%)

SD:Standart Deviation,FUFA: 5 Fluorouracil-Folic Acid

significant correlations were found between dissection type, number of lymph nodes removed or involved and survival.

**Figure 1.** Log rank analyze for dissection type.



Among the 22 patients that have observed relapse during the follow up period, 5 (8%) patients of them were locoregionally recurred as the first site of relapse. Recurrent lesions were embedded to RT plans and new plan was generated as detailed in methodology section (Figure 2). In this context, we identified 3 nodal and 2 local recurrences with one pathologic confirmation, rest evaluated by the radiologist without biopsies. All of the locoregionally recurred patients were underwent D2 node dissection. Two nodal recurrences were determined in group 2 (covered by 95% and 100% isodose) and one in group 3 (covered by 20% isodose) LN groups. Local recurrences were found in anastomosis site (biopsy confirmed and covered by 90% isodose) and peritoneal surface (covered by 50% isodose) (Table 2).

**DISCUSSION**

In current study, 62 curatively resected gastric carcinoma patients were examined in terms of

recurrence pattern and survival. The 3 and 5-year OS were 71% and 55% respectively, and better with D2 dissection without statistical significance. During the 18 months follow up, 5 (8%) patients had locoregional failure as the first site of relapse. All of them had R0 and D2 resection. Nodal recurrences were in group 2 in 2 patients (covered by 95% and 100% isodose) and group 3 in one patient (covered by 20% isodose). One of the local recurrences was detected in anastomosis site (biopsy confirmed and covered by 90% isodose) and the other one was found on peritoneal surface (covered by 50% isodose) when compared to their initial RT volumes.

Survival rates after surgery alone for gastric carcinoma are 34% to 70% for patients in stages 1 and 2 and 7% to 20% for stages 3 and 4 (15, 16). Take into consideration the recent merits in survival that have been accomplished with postoperative CRT and perioperative chemotherapy, adjuvant treatment is the standard of care for patients with resectable gastric cancer more advanced than stage T2N0 (10, 11, 17). The Intergroup 0116 randomized study of 556 patients with resectable gastric adenocarcinoma illustrated that postoperative CRT with FUFA improved 5-year overall survival (40% vs 22%) and locoregional recurrence rate (LRR) (19% vs 29%) compared with surgery only. Despite the use of CRT, LRR was found 19% for five years (10, 11). We have found a 5-year OS of 55% in our relatively small number of curatively resected gastric carcinoma patients.

Survival benefit with extended dissection is a subject of debate between western and eastern World. There is quite evidence demonstrating survival benefit with D2 dissection in eastern world (18). Dutch trial was reported in 2010 and may change the Western opinion regarding the question of long survival benefit of D2 versus D1 lymphadenectomy (19). Inspection of the 15-year survival curve discloses an initial dip in the D2 arm mirroring the higher perioperative mortality, but between years 4 and 5 the

survival curves cross and continue to separate with 8% higher survival in the D2 arm at 15 years (29 vs. 21%;  $P = 0.34$ ). This result is not statistically significant, but the crossing of the survival curves recommend that there may be a long-term survival profit to D2 lymphadenectomy that was able to equate for the initial higher perioperative mortality in this group. Patients undergoing D2 lymphadenectomy had a significantly lower ratio of disease-specific death (37 vs. 48%;  $P = 0.01$ ) than those dissected D1 lymphadenectomy. More patients in the D1 arm had local recurrence at the time of death (41 vs. 30%,  $P < 0.05$ ) (18).

Since INT 0116 was mainly criticized for its majority of D1 dissected patients, the role of RT in D1 versus D2 dissected group was questioned. Dikens et al. (20) compared the outcome of the patients who received CRT with the historical surgery only group randomly assigned to either D1 or D2 dissection. They found out local recurrence rate after 2 years was significantly higher in surgery solely group (17% vs 5%;  $p = .0015$ ). But this did not turn into a significant survival difference, 71% vs 67% at 2-years. Subgroup analysis of the study revealed that local recurrence rate was significantly lower in D1 dissected CRT group compared with D1 resection alone group (2% vs 8%  $p = .001$ ) but benefit was not translated to survival. There were no differences between D2 dissected CRT group compared to D2 dissection alone in respect of local recurrence rate (12% vs 13%) (20).

RT profit in D2 dissected group was the unique property of the Artist trial (21) which randomly allotted pathologically staged IB to IV (M0) gastric cancer patients to adjuvant chemotherapy encompassing six cycles of capecitabine and cisplatin (XP) or 2 cycles of XP before and after concurrent capecitabine and RT (XPRT). After a median follow-up of 7 years, updated analysis demonstrated that there was still not a significant difference in DFS for the whole study population nevertheless, the node-positive patients treated on the XPRT arm

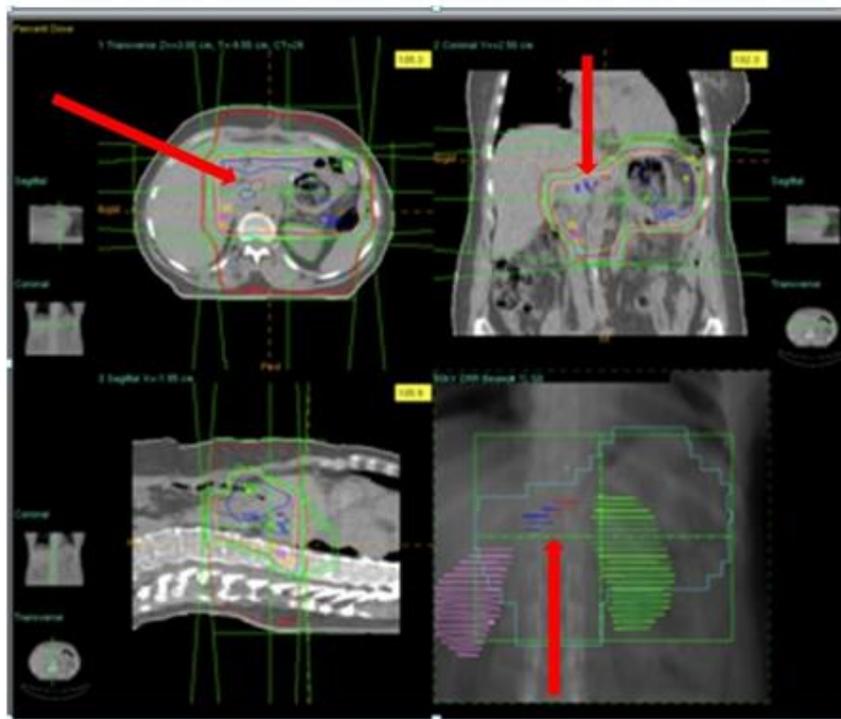
**Table 2.** Characteristics of Recurrent Patients

Patient	Gastrectomy	Dissection	Margin status	Stage	Recurrence Site	Coverage
1	Total	D2	NM	3B(T3 N3a)	NS, Group 2	%100
2	Subtotal	D2	NM	3B(T4a N2)	NS, Group2	%95
3	Total	D2	NM	3C(T4a N3a)	Surgical bed	%50
4	Total	D2	NM	3A(T4a N1)	NS, Group3	%20
5	Total	D2	CM	3A(T4a N1)	Anastomosis Site	%90

NM: Negative Margin, CM: Close Margin, NS: Nodal Site

preserved a DFS merit (XP arm, 72% vs XPRT arm, 76%;  $p=.04$ ). This study showed that even in D2 dissection RT can provide some benefit over chemotherapy in certain subgroups (21, 22). In our trial, 34 patients (%54.8) have undergone D2 LN dissection. We also compared the survival rates between dissection groups, and found better outcome with D2 dissection without statistical significance. This may be because of relatively small number of patients and we analyzed.

Based on these results, investigators of Artist trial designed another study (23) to establish optimal adjuvant RT indications and target volumes after D2 gastrectomy by employing the data of this trial. They assessed the effect of adjuvant RT on recurrence at each locoregional subsite and examined which subgroups received the most benefit via comparing failure patterns. Forty four (9.6%; 29 in XP, 15 in XPRT;  $P = 0.03$ ) patients evolved local and/or regional recurrence in their series



**Figure 2.** Nodal recurrence of a patient in group 2 lymph nodes (95% isodose). Red arrows indicate the nodal recurrences.

of 458 patients. Among all patients, local recurrence developed in 22 patients (4.8%, 11 in the XP arm; 11 in the XPRT arm). The local recurrence rate (4.8%) did not differ between arms. Within 28 patients with regional recurrence, 23 were in the XP arm and 5 were in the XPRT arm, a difference that was significant ( $P < 0.001$ ). Most regional recurrences (25 of 28, 89.3%) evolved in group 3 LNs despite D2 lymphadenectomy. Only four (0.9%) recurrences took place in group 2 LNs which illustrates us that adjuvant RT primarily affects regional recurrence, mostly in group 3 LNs; Contrary, local failure was not significantly affected by RT (23). In the present study, only one of the 5 locoregional recurrence (20%) was found in group 3 LN region. This can be explained with small sample size and small amount of events of our trial.

Lim et al. (24) examined the recurrence pattern of D2 dissected R0 patients who received CRT according to INT 0116. The 5-year OS and DFS rates were 62% and 58%. During the follow-up period, 13/114 (5%) isolated loco regional recurrence occurred with traditional parallel opposed field technique which is less than our series (24). Fewer patient numbers and or RT technique may also be the reason for this difference.

Conrad et al. (25) examined the recurrence pattern of 197 patients, 7% of all ( $n=14$ ) had isolated locoregional recurrence but only 9 of them could be reviewed with respect to RT volumes. Recurrences encompassing by the 90% isodose line were considered to be in field, 50-90% isodose line were marginal. If it was not covered by 50%, it is considered out of field. In this context; 5 were in field, 2 were marginal and 2 were out of field (25). The current study is the first study analyzing the detailed localization of recurrences individually with reviewing the coverage of the isodoses matching with the RT planning CT in 3D. We had a total of 5 locoregional recurrences, 3 were in field, one was marginal and 1 was out of field. Out of field relapse was in group 3 nodal station which is not routinely included to PTV. This

brings the idea of including this region to target volume but total number of patients analyzed is very low to draw such firm conclusions. Furthermore, this study demonstrated that marginal relapse could have been remained in RT field in traditional parallel opposed RT plans.

In this study, we aimed to explore locoregional regions individually to understand the patterns of failure in gastric cancer patients treated with adjuvant CRT. One marginal and one out of field recurrence shows that arrangement of treatment portal fields and delineating the target volumes needs careful attention to avoid locoregional recurrences especially while using IMRT technique. Escalating the doses in some locoregional regions up to the pathological and radiological findings may decrease infield recurrences respect to the critical organs. But we need further studies to increase the doses in some regions routinely.

Reviewed hospitals in this study are low income centers by less than 50 gastrectomies per year. This may also have caused selection bias in some extent.

### Conclusion

Delineation of RT target volume is highly essential when using conformal techniques in postoperative setting. Identification of the local recurrence site may be helpful in determining the RT target volume for minimizing locoregional recurrences.

### Çıkar Çatışması: Yok

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