

EVALUATION OF THE SURGICAL MARGIN SHRINKAGE AFTER RESECTION AND FORMALIN FIXATION IN ESOPHAGUS - GASTRIC MALIGNANCY AND TO CREATE A CORRECTION FACTOR: A PROSPECTIVE STUDY

ÖZOFAGUS-MİDE MALİGNİTELERİNDE REZEKSİYONDAN VE FORMOL FİKSASYONUNDAN SONRA OLUŞAN CERRAHİ SINIR KISALMALARININ DEĞERLENDİRİLMESİ VE DÜZELTME FAKTÖRÜ YARATILMASI: PROSPEKTİF BİR ÇALIŞMA

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SUMMARY

Introduction: To evaluate shrinkage of surgical margins between in-vivo measurements and the final histopathological examination in patients undergoing surgical treatment for esophageal or gastric malignancies and creating a correction factor for adequate resection margin.

Material and Method: In patients with esophageal and gastric malignancies, proximal and distal surgical margins were measured from the macroscopic serosal tumor margin in normal anatomic position prior to resection. The specimens were sent to the histopathology laboratory. The distance of the tumor to the proximal and distal surgical margins were measured by the pathologist before formalin fixation. After specimens were fixed for 24 hours with 10% formaldehyde, measurements were repeated by the same pathologist. Paraffin block sections of all specimens were evaluated histopathologically and measurements were recorded by selecting the paraffin block representing the closest surgical margin of the specimen.

Results: Twenty-five patients were included in the study. The median values of the proximal surgical margin before resection, before fixation, 24 hours after fixation and after histopathological examination were 8cm (min-max:3-23.5cm), 5.4 cm (min-max:0.7-19cm), 4.3cm (min-max: 0-14cm), 3.5 cm (min-max:0-14.5cm) respectively. For distal surgical margin, median values were 6 cm (min-max:2-18.5cm), 5.8 cm (min-max:2-16cm), 5 cm (min-max:1-14cm), 5 cm (min-max:0-15cm) respectively. The correction factor calculated for the shrinkage of proximal and distal surgical margin from pre-resection to final histopathological examination was 1.88(p<0,001) and 1.4 (p<0,001), respectively.

Conclusions: Creation and use of correction factors to predict the shrinkage of surgical margins in curative surgeries for esophageal and gastric malignancies will be effective in providing adequate resection margin.

ÖZ

Giriş: Cerrahi tedavi uygulanan özofagus-mide malignitelerinde rezeksiyon öncesi ile en son mikroskopik inceleme arasındaki cerrahi sınır kısalmalarını değerlendirmek ve yeterli rezeksiyon marjini için düzeltme faktörü yaratmaktır.

Gereç ve yöntem: Özofagus ve mide maligniteli hastalarda ameliyat esnasında rezeksiyondan önce normal anatomik konumda makroskopik serozal tümör sınırından proksimal ve distal cerrahi sınırlar ölçüldü. Spesmenler patoloji laboratuvarına gönderildi ve fiksatif konulmadan önce açılarak tümör boyutu ile tümörün proksimal ve distal cerrahi sınırlara uzaklığı patoloj tarafından ölçüldü. Spesmenler %10'luk formaldehit ile 24 saat tespit edildikten sonra tekrar aynı patoloj tarafından ölçümler tekrarlandı. Tüm olguların parafin blok kesitleri histopatolojik olarak değerlendirildi, en yakın cerrahi sınırı temsil eden parafin blok seçilerek kayıt altına alındı.

Bulgular: Toplam 25 hasta çalışmaya dahil edildi. Proksimal cerrahi sınır için rezeksiyon öncesi, fiksasyon öncesi, fiksasyon sonrası 24 saat ve histopatolojik inceleme sonrası medyan değerler sırası ile 8 cm (min-max:3-23.5cm), 5.4 cm (min-max:0.7-19.cm), 4.3 cm (min-max:0-14 cm), 3.5 cm (min-max:0-4.5cm) olarak bulundu. Distal cerrahi sınır için bu değerler sırası ile 6 cm (min-max:2-18.5cm), 5.8 cm (min-max:2-16cm), 5 cm (min-max:1-14 cm), 5 cm (min-max:0-15cm) olarak bulundu. Proksimal ve distal cerrahi sınır için rezeksiyon öncesi ve nihai patolojik inceleme arasında hesaplanan düzeltme faktörü proksimal ve distal rezeksiyon marjı için sırasıyla 1.8 ve 1.4 olarak bulundu.

Sonuç: Özofagus ve mide maligniteleri için yapılacak küratif cerrahilerde cerrahi sınırlardaki kısalmaları önceden tahmin etmek için düzeltme faktörlerinin yaratılması ve kullanılması yeterli rezeksiyon marjini sağlamada etkili olacaktır.

INTRODUCTION

Surgical treatment is the cornerstone of gastric and esophagogastric junction malignancies. Surgical treatment includes D2 lymphadenectomy with total or subtotal gastrectomy for potentially curable T2-T4 tumors and lymph node + patients. Other resection and lymphadenectomy options should be for only palliative interventions for tumors in these stages. Chemotherapy and targeted therapies are only adjuvant therapies. Adequate resection margin (RM) must be provided for curative surgery in gastric cancers. For T1 tumors 2 cm RM should be provided. At least 3 cm proximal margin (PM) for T2-T4 tumors with expansive growth pattern (Type 1-2), and at least 5 cm PM for tumors with infiltrative growth pattern (Type 3-4) is recommended. Frozen section examination of the proximal margin is recommended when safe surgical margin cannot be obtained. For tumors infiltrating the esophagus, a 5 cm margin is not required, but frozen section examination of the RM is recommended. A macroscopic surgical margin of 2 centimeters is recommended for non-invasive tumors of the duodenum and 3 centimeters for invasive tumors(1). As in the surgical treatment of gastric cancer, the main target in other oncological surgeries is removing the tumor in such a way as to ensure a proper RM. RM plays an important role in prognosis. Removal of tumors with inadequate RM leads to anastomosis leakage and recurrences. Patients

with tumor cells at the surgical margin may also require additional surgical treatment or postoperative radiotherapy (2-5). Although it is not clear that either the resection margin determined during the surgery or by the histopathological examination will be taken into consideration, it is a fact that the final microscopic surgical margin is generally accepted. This leads to some disagreements between surgeons and pathologists. Immediately after resection and after formalin fixation, contractility and shrinkage in tissues are well known. The aim of this study was to establish a coefficient capable of predicting contractility and shortening in esophageal and gastric cancer specimens resected surgically and providing adequate final pathological microscopic RM to protect patients from the adverse effects of inadequate RM.

MATERIAL AND METHODS

The study was conducted prospectively and 25 patients who underwent surgery for esophageal and gastric malignancy were included. The operations which were performed for the malignancy groups were standardized and the were performed by specific surgeons. Patients with recurrent tumors, patients with remnant gastric cancer, patients with synchronous tumors and patients with tumors which 24-hour fixation period not able to provided for any reason were excluded from the study. Informed consent was

obtained from all patients and the study was conducted in accordance with the Helsinki Ethical Principles. Ethics approval was obtained from the Health Sciences University, Izmir Bozyaka Training and Research Hospital Ethics Committee for the study. Proximal and distal surgical margins and largest tumor size were measured in normal anatomic position from the end point of the tumor before resection (in situ measurement) in patients underwent surgery for esophageal or gastric malignancy (adenocarcinoma, squamous cell carcinoma, gastrointestinal stromal tumor, neuroendocrine tumor, etc.). Immediately after resection, specimens were sent to the histopathology laboratory. Size of tumor and the distance of the tumor from the proximal and distal surgical margins were measured by the pathologist before formalin fixation. Paraffin block sections of all cases were evaluated histopathologically. Measurements were recorded by selecting the paraffin block representing the closest surgical margin of the cases. The total shortening from the in situ measurement in the normal anatomical position without any tension force to the final histopathological border after the fixation was considered as shrinkage. The correction factor was found with the following formula: Correction factor = RM measured during the operation / RM found in histopathological examination.

Statistical Analysis; Data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill). Continuous data of patients were given as mean \pm standard deviation and median (minimum-maximum) and categorical data were given as percentage. Kruskal Wallis test was used to compare categorical variables between groups. Statistical significance was accepted as $p < 0.05$.

RESULTS

The mean age of the patients was 66 (\pm 10,2) years. The distribution of patients according to gender, tumor localization and type of surgery are shown in Table 1. According to the histological examination results, 18 (72%) patients had gastric adenocarcinoma, 3 (12%) had esophageal squamous cell carcinoma, 1 (4%) had a gastric neuroendocrine tumor and 3 (12%) had a stomach neuroendocrine tumor and gastric adenocarcinoma together. The pTNM stages of the cases were respectively; 19

patients with gastric adenocarcinoma were stage 3, 1 patient was stage 2, 1 patient was stage 1; 2 patients with squamous cell carcinoma were stage 3, 1 patient was stage 1 and 1 patient with neuroendocrine carcinoma was stage 3. The median (min-max) value of the total number of resected lymph nodes was 25 (0-82) and the median (min-max) value of the number of metastatic lymph nodes was 6 (0-57). The median values of the proximal surgical margin before resection, before fixation, 24 hours after fixation and after histopathological examination were 8cm (min-max:3-23.5cm), 5.4 cm (min-max:0.7-19cm), 4.3cm (min-max: 0-14cm), 3.5 cm (min-max:0-14.5cm) respectively. For distal surgical margin, median values were 6 cm (min-max:2-18.5cm), 5.8 cm (min-max:2-16cm), 5 cm (min-max:1-14cm), 5 cm (min-max:0-15cm) respectively (Table2).

Table 1. Distribution of 25 patients by gender, tumor localization and type of surgery

Gender	
Female	6 (24%)
Male	19 (76%)
Localization of tumor	
Distal esophagus	4(16%)
Upper 1/3 stomach	7 (28%)
Middle 1/3 stomach	4 (16%)
Distal 1/3 stomach	10 (40%)
Operation types	
Ivor-lewis operation	3 (12%)
Proximal subtotal gastrectomy	2 (8%)
Total gastrectomy	15 (60%)
Distal subtotal gastrectomy	5 (20%)

Shrinkages of the proximal surgical margin and distal surgical margin before fixation, after fixation and histopathological examination were compared according to the tumor localization. There was no statistically significant difference between the groups ($p \leq 0.05$). The median (min-max) values of proximal and distal surgical margin shrinkages are shown in Table 3 and Table 4. A correction factor predicting the shortening of the proximal and distal surgical margins between the per-operative measurements and the final pathological examination was calculated. This rate was 1.88 for proximal surgical margin and 1.4 for distal surgical margin and both were statistically significant. The correction factor calculated for the shrinkage of proximal and distal surgical margin from in situ to final histopathological examination was 1.8 and 1.4 respectively.

Table 2. Measurements of proximal surgical margin, tumor size and distal surgical margin

		Proximal surgical margin(cm)	Distal surgical margin(cm)	Tumor size(cm)
Measurement time				
Before resection	mean(\pm)	8,5(\pm 5,2)	8,4(\pm 4,8)	5,6(\pm 2,2)
	median(min- max)	8(3-23,5)	6(2-18,5)	5 (1,5-10)
Before fixation	mean(\pm)	6,2(\pm 4,3)	7,5(\pm 4,6)	6,6(\pm 2,1)
	median(min- max)	5,4 (0,7-19,5)	5,8 (2-16)	6,1 (2-15)
After fixation	mean(\pm)	4,9(\pm 3,6)	6(\pm 3,7)	5,4(\pm 2,1)
	median(min- max)	4,3 (0-14)	5 (1-14)	5 (1-10)
Final histopathologic examination	mean(\pm)	4,5(\pm 3,5)	6(\pm 4,3)	6(\pm 2,6)
	median(min- max)	3,5(0-14,5)	5(0-15)	6(1-12)

Table 3. The median (min-max) shrinkages of the proximal surgical margin

Localization	Before fixation	After fixation	Final histopathologic examination
	p=0.997	p=0.918	p=0.324
Distal esophagus	-1 (-7,5, 0)	-2 (-8,5, -2)	-2 (-7,3, 1)
Upper 1/3 stomach	-2,3 (0, -7,3)	-3,5 (-8, -0,5)	-4 (-8, 1)
Middle 1/3 stomach	-1 (-4, 0)	-2,5 (-6, -1)	-1,8 (-6,5, -1)
Distal 1/3 stomach	-2,5 (-10, 0,5)	-4 (-11,5, -1,2)	-4,5 (-11,5, -1,5)

Table 4. The median (min-max) shrinkages of the distal surgical margin

Localization	Before fixation	After fixation	Final histopathologic examination
	p=0.571	p=0.646	p=0.797
Distal esophagus	0 (-0,5, 0)	-2 (-3, -0,5)	-0,9 (-2, 1)
Upper 1/3 stomach	-0,3 (-4,5, 0)	-1,8 (-7,5, 0,5)	-1 (-7,5, 7)
Middle 1/3 stomach	0,75 (-3,5, 0)	-1,8 (-4, -1)	-1,8 (-4, -1)
Distal 1/3 stomach	0 (-3, 6)	-1 (-8, -6)	-1 (-8, 2,5)

DISCUSSION

It is a known fact that there are differences between RM measured during the surgery and the RM after histopathological examination. There are limited number of studies in the literature with a few cases searching these differences.

Siu et al. reported 44% and 54% shrinkages in proximal and distal RM respectively after resection of the esophagus in patients with esophageal cancer. After fixation, these rates were 32% and 39%, respectively (6). In our study, these rates were 27%, 11% before fixation and 43%, 29% after fixation for proximal and distal RM respectively. Wang et al. reported correction factor for RM in 52 digestive tract cancer patients, 27 of which were gastric cancer. They measured the specimens 3-5 minutes after resection and 12-24 hours after formalin fixation. They found correction factor of proximal and distal RM that 1.80 and 2.22 for esophagus, 1.16 and 1.43 for stomach, respectively (4). In our study, these rates were 1.8 and 1.4 for the proximal and distal RM, respectively. On the

other hand, Khoshnevis et al. reported proximal RM shrinkage of 10 esophageal cancer patients after 24, 48 and 72 hours after 10% formalin fixation up to 27%, 33% and 38%, respectively (7).

Similar studies have been made for other organ cancers. Gökoğlu et al. suggested that the length of resection required to provide a surgical margin of 5 mm in sheep tongue should be 7-8 mm and the correction factor was 1.42 (8). In a retrospective study of 50 cases by Yeap et al., mastectomy specimens showed a 33% shrinkage in RM after fixation and 58% shrinkage in wide excision margins (9). Dauendorffer et al. reported that skin excision specimens were shrunk by 16% in length and 18% in width after formalin fixation in a study involving 82 cases (10). Goldstein et al. presented their studies to reveal the shrinkages in RM measured by surgeons (in vivo) and pathologists (in vitro) in 26 sigmoid colon and rectum specimens. They reported a 40% reduction in in-vivo length after 10-20 minutes after removal and a 57% reduction in in-vivo length after fixation (11).

Another remarkable point is whether there is a change in the T stage of the tumor after fixation of the specimens. Hsu et al. found migration from T2 stage to T1 stage after fixation in a considerable group in their study with non-small cell lung cancer patients (12). Similarly, in a retrospective study with thyroid cancer patients Lacout et al. emphasized that ultrasonographic T measurement is different from pathological evaluation and they stated that prospective studies are needed (13). Tran et al. reported that the size of the radiological tumor was 12.1% higher than the fresh tumor size, while the fresh tumor size was 4.6% higher than size after the fixation and size after the fixation was 7.1% higher than size after histopathologic examination. In addition, pT1b was shifted to pT1a in two cases (14).

Limitations of this study, cT staging could not be performed exactly, so pT stages could not be compared with cT stages. Another limitation is that since the mucosal border of the tumor may be different, than macroscopic serosal border. We have resected by measuring from the macroscopic serosal tumor border. However, our

conditions were not suitable for the detection of mucosal border by endoscopy during surgery. Due to the lack of cases and heterogeneous patient populations, the stomach and esophagus sections for the proximal surgical margin and the stomach and duodenum sections for distal surgical margins could not be evaluated separately.

CONCLUSION

Our study showed that there was a significant difference in the proximal and distal RMs of patients with esophageal and gastric malignancies between measurements before resection and after resection and use of correction factors to predict the shrinkage of surgical margins in curative surgeries will be effective in providing adequate resection margin. Frozen section examination of the proximal margin is recommended when safe surgical margin cannot be obtained. Emphasizing the correction factors which were created as a result of prospective studies with large number of patients will protect the patients from the negative effects of inadequate resection.

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