REVIEW ARTICLE

Surgical safety margin of gastroenterological cancer surgery: A truth or a dream?

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Summary Most surgeons dream about performing an extensive resection with a wide resection margin and extensive lymph nodes dissection, which will yield a favorable prognosis. Previous studies have reported varying lengths of the margins based on different clinical profiles. The so-called safety margin is not completely safe because limited scientific evidence exists for nonrecurrence, even after the patient has had a pathological examination to prove a negative cancer invasion at the resection margin. The safety margins for malignancy are different in the esophagus, stomach, colorectum, liver, and others because of the different modes of carcinogenesis and variable paths of recurrence. However, a minimally acceptable margin length can be defined because the margin is destroyed during operative dissection or shortened after formalin fixation for tissue assessment during pathological diagnosis. The currently available data for supporting the reality of a true negative or true positive invasion at the resection margin could be presumed by gross findings of a solid tumor. A safety margin for esophageal, gastric, liver, and colorectal cancer could be 0.1, 2–4, 2, and 1–3 cm, respectively. A dream to have a real safety surgical margin to achieve better surgical outcome is a challenge for any gastroenterological surgeon. However, a complete safety margin may not always be realized because it is impossible to have a true negative margin from surgical equipment and pathological tissue process. Copyright © 2013, Taiwan Surgical Association. Published by Elsevier Taiwan LLC. All rights reserved.

1. Introduction

The role of a surgical margin in surgical oncology has always been discussed with regard to the tumor recurrence and survival rate in gastrointestinal cancer surgery. Previous reports have suggested that extensive operation with a wide resection margin and extensive lymph node dissection will probably result in a better prognosis.1–4 According to
the “seed-and-soil theory”, during the carcinogenesis of liver tumor, less liver parenchyma will mean less likelihood of recurrence. As a result, extensive liver resection for primary liver cancer is usually encouraged if liver function is preserved.\(^5^{–7}\) In the report by Poon et al,\(^8\) extended hepatic resection for hepatocellular carcinoma (HCC) with cirrhosis needed to be justified depending on the preserved liver function. Besides, there were no significant differences in the incidence of hepatic failure, complication rate, and resection margin width between the groups undergoing extended or lesser extended hepatectomy for HCC. The role of the surgical margin width in a hepatectomy for HCC was explained by Shimada et al,\(^9\) and it was suggested to secure a surgical margin >10 mm in young patients without hepatitis C virus infection and/or a tumor size of 25 mm or larger after a macroscopic curative hepatectomy to achieve long-term disease-free survival.

However, differences exist with regard to the role of surgical margin. For example, the “1-cm rule” for distal rectal cancer surgery refers to distal bowel margin as measured by surgeons on the fresh anatomically restored ex vivo condition, as reported by Bujko et al.\(^10\) The bias in measurement could be induced by the measuring pathologist on either the fresh tissue or on formalin-fixed specimens. Because of the bowel shrinkage occurring soon after the removal from the patient’s abdomen and the additional shrinkage occurring after fixation, correction factors have been proposed to account for the shrinkage of the distal margin. In addition, because the measurements were based on histological assessment during pathologic evaluation and not routinely by the surgeon’s operative findings, the results of the previous report\(^10\) should be considered taking this limitation into account, which may induce a potential source of bias.

Safety surgical margin of each organ in gastroenterologic cancer will have different recurrence and/or survival rates. In addition, the length of safety surgical margin cannot be firmly set with regard to the various organs. Actually, no impairment in the oncologic safety margin is expected owing to the differences that exist, as a negative or an ultraclosed negative will yield a totally different surgical outcome.

2. Surgical margin in esophagus cancer

The prognostic role and definition of the circumferential resection margin (CRM) involvement in operable esophageal cancer remain controversial. The College of American Pathologists and Royal College of Pathologists define CRM involvement as a tumor found at the cut resection margin and a tumor within 1 mm of the cut margin, respectively. A systematic review and meta-analysis was performed to determine the influence of CRM involvement on survival in operable esophageal cancer.\(^11\) In this previous study by Chan et al, 2433 patients with esophageal cancer who had undergone potentially curative esophagectomy were analyzed in 14 reports. The CRM involvement between 0.1 and 1 mm was associated with a significantly higher 5-year mortality rate than the CRM-negative status \((p < 0.001)\). Thus it was concluded that CRM involvement is an important predictor of esophageal cancer prognosis. Microscopic tumor infiltration of the resection margin after esophageal resection is implicated to influence anastomotic leakage, tumor recurrence rates, and long-term survival. Law et al compared patients with tumor infiltration of resection margin \((RM^+\)) and those without infiltration \((RM^-)\).\(^12\) Of the total 604 patients analyzed in the study, anastomotic recurrences developed in 10.3% of the patients in the RM+ group and in 4.9% of the patients in the RM– group without significant difference. Although a positive margin did not increase anastomotic recurrence, median survival time was significant different. However, in another study by Dexter et al,\(^13\) the odds ratio for the risk of dying from esophageal cancer was 2.08 when the CRM was involved \((p = 0.013)\). Therefore, the presence of tumor within 1 mm of the circumferential margin following potentially curative resection for esophageal carcinoma is an important independent prognostic variable, and thus, it should be routinely reported.

3. Surgical margin in gastric cancer

The effect of positive or negative resection margin on the prognosis of gastric cancer was recognized and debated for decades. In a retrospective study by Chen et al,\(^14\) 64 advanced gastric cancer patients with positive resection margin after potentially curative resection were investigated for the prognostic effect of postoperative resection margin status for intraoperative positive resection margins. The survival between those patients who were re-excised to a negative resection margin and those who were left with positive resection margin was compared. The median survival in the positive resection margin group was 17.0 months as compared with 23.0 months in the negative resection margin group \((p = 0.045)\). Therefore, routine frozen section examination of the resection margins should be mandatory in all advanced gastric cancer patients undergoing potentially curative surgery. However, it is necessary to discuss how far is adequate to avoid the positive resection margin. In fact, the incidence of infiltration of the proximal edge was significantly higher when the tumor penetrated the serosa layer or spread beyond it than when the lesion was confined to the mucosal, submucosal, or muscular layer.\(^1\) With reference to the length of the resection margin, no involvement was found when the cranial distance between the lesion and the line of resection was \(\geq 6\) cm. Proximal or distal infiltration for a distance \(>3\) cm did not occur in patients with lesions confined to the mucosal, submucosal, and muscular layers. With regard to the length of the resection margin, no involvement was found when the cranial distance between the lesion and the line of transection exceeded 2 cm in patients with orally well-defined-type esophageal invasion. However, in patients with orally ill-defined type, transection with a distance \(>4\) cm commonly guarantees safety of the proximal margin, except for cases with lymphatic invasion.\(^15\) These data provide a gastric surgeon with a rational basis for assessing the extent of resection while performing gastrectomy for gastric cancer.
In the case of adenocarcinoma of the gastroesophageal junction (GEJ), the length of esophageal resection or the operative approach influences the outcome of the patients. A multivariable analysis in patients who underwent R0 resection with lymph nodes examinations revealed that the number of positive lymph nodes, T stage, tumor grade, and ex vivo proximal margin length >3.8 cm were independent prognostic factors. In addition, the study reported that in patients not receiving neoadjuvant therapy, the goal for patients with adenocarcinoma of the GEJ should be R0 resection including at least 15 lymph nodes, preferably with 5 cm of grossly normal in situ proximal esophagus for those with six or less positive lymph nodes. Therefore, in order to achieve better results it should be individualized to decide the esophageal resection margin and operative approach.

4. Surgical margin in primary and secondary liver cancer

4.1. HCC

There was no significant difference on the overall survival rate and disease-free survival rate in patients with HCC who received major or limited open resection. Therefore, major heptectomy was not recommended for patients with solitary small HCC measuring 3 cm or less in diameter in the series of Shimada et al. In a retrospective study on patients who underwent laparoscopic liver resection for HCC, no significant difference was observed in the overall survival rate between the major heptectomy (2 segments or more) and the minor heptectomy group (1 segment or less). However, postoperative tumor recurrence was commonly found in patients with HCC, and no promising methods for prevention of recurrence exist. The effect of surgical resections with wide margins on tumor recurrence and survival rates remains controversial. In a study by Yu et al., HCC patients treated by open resection with a tumor resection margin <5 mm had a poorer prognosis of the intrahepatic recurrence. The influence of surgical safety margin while performing traditional open laparotomy was also discussed in a few studies. Without any doubt, laparoscopic liver surgery has advantages over the traditional open procedure in selected patients. However, owing to the lack of an operator’s finger feeling during a laparoscopic approach, it is somewhat difficult to keep a safety margin far from the resection plane during liver dissection. In an unpublished study, the 1-, 3-, and 5-year survival rates were 84.2%, 67.3%, 57.7% and 93.3%, 86.7%, 78.0% for operating on HCC patients with safety margins of 5–9 mm or ≥10 mm, respectively, with a nonsignificant difference ($p = 0.139$). Our retrograde evaluation of the clinical significance in those patients who underwent either laparoscopic or traditional liver resection for tumor located at the anterior aspects of HCC revealed a nonsignificant difference based on case-matched analysis. Therefore, based on previous reports and our experiences, it can be concluded that a surgical margin set at the level of 1 cm will be adequate for liver cancer surgery. In a prospective randomized trial, Shi et al. compared the efficacy and safety of partial heptectomy aiming grossly at a wide and narrow resection margin in patients with macroscopically solitary HCC. The study results revealed that a resection margin aiming grossly at 2 cm efficaciously decreased postoperative recurrence rate and improved survival outcomes when compared with a gross resection margin aiming at 1 cm, especially for HCCs measuring ≤2 cm. However, surgeons usually hesitate to perform major liver resection in patients with severe liver cirrhosis, because the patients could die due to poor remnant liver function. In situations where a tumor is located near the area of porta hepatitis or close to the main blood vessels or bile duct, it is impossible to have the surgical margin >1 cm. Qin and Tang reported no significant difference in the survival rates between the HCC patients who received different extensions of liver resection. Therefore, it is not necessary to try to have an extended safety surgical margin for patients with obvious liver cirrhosis. It is, however, true that a wide resection margin will minimize potential microscopic invasion, subsequently resulting in better survival rates.

4.2. Cholangiocellular carcinoma

Theoretically, an anatomic liver resection with a wider resection margin gives a higher potential for curing HCC or cholangiocellular carcinoma (CCC). However, preserving nontumor liver parenchyma is an important issue to avoid postoperative hepatic failure, especially in patients with cirrhotic liver. The optimal liver resection margin for CCC is still controversial. A resection margin of 2 cm is associated with a decreased postoperative recurrence rate and improved survival outcomes. Hepatic resection, whenever technically possible, should be enforced because the preoperative pathological diagnosis of HCC or CCC is difficult and the next treatment option needs to be clear. However, the expected narrow hepatic resection margins should not discourage patients from undergoing potentially curative surgery or hoping for long-term survival. In case of hilar cholangiocarcinoma, a radical resection has been shown to be the only parameter with a significant impact on survival. Extended heptectomy seems to give the best oncologic results. A surgical margin <1 cm after the resection should not be used as an exclusion criterion for resection and it will not impair patients’ prognosis. Resection should be performed irrespective of the width of the surgical margin. In another study by Ribero and the Italian Intrahepatic Cholangiocarcinoma Study Group, a total of 434 patients were included and underwent a major or extended heptectomy (70.0%) and a systematic lymphadenectomy (62.2%). The median time of survival in these patients was 39 months, and the 5-year survival rate was 39.8%. Conversely, survival was not influenced by the width of a negative resection margin ($p = 0.61$).

4.3. Liver metastasis tumor from colorectal cancer

With regard to the safety surgical margin for metastatic liver tumor from colorectal cancer, a safety margin ≤1 cm is generally accepted in liver surgery for colorectal metastases. However, modern methods of liver parenchyma dissection may allow for a reduction in this distance and a 1–3-mm margin is considered safe. In the study by
Kopke et al, 333 patients were included in a multicenter trial after resection of colorectal liver metastases.33 An analysis of different groups denoting the extent of resection margin [≥10, 6–9, 3–5, 1–2, and 0 mm (R1)] indicated that a margin of 1–2 mm leads to a significantly reduced median hepatic recurrence-free survival of 20 months (p = 0.004) and recurrence-free survival of 19 months (p = 0.011). Surgical margins were significantly reduced in simultaneous resections of four or more liver metastases and in cases in which metastatic infiltration of central liver segments was present. The indication for resection of metastases can also be safely extended to tumors that are located within 1 cm to nonresectable structures.

Patients who fail to achieve 1-cm margin are routinely treated with edge cryotherapy, as reported by Hou et al.32 They tried to evaluate the benefit of edge cryotherapy on survival in 608 patients with optimal margins <1 mm. As long as the surgical margin is clear macroscopically, the width of the microscopic margin does not affect the patient’s survival. In patients with suboptimal margins, the additional edge cryotherapy will improve the prospect for long-term survival and may lower recurrence risk. If an unsafe surgical margin is noted during the perioperative period, we recommend using cryotherapy or performing cautery with heat probe to treat the risky margin in order to achieve a better prognosis. Table 1 presents the results of surgical margin for cancer surgery from the literature.

### 5. Surgical margin in colorectal cancer

The Japanese general rules for clinical and pathologic studies on cancer of the colon, rectum, and anus state that a 3-cm distal resection margin is needed in rectosigmoid cancer and rectal cancer with a distal edge above the peritoneal reflection, and a 2-cm margin is needed for rectal cancer with a distal edge below the peritoneal reflection. However, it was suggested that a distal margin of at least 5 mm with a negative resection margin on frozen section examination does not reduce oncological safety in patients with rectal cancer who receive preoperative or postoperative chemoradiotherapy. The length will be shorter if the patient undergoes additional treatment along with preoperative radiation. However, there is no excuse for the extension of the resection of mesocolon no matter how short the resection margin is from the tumor.

#### Table 1 Surgical margin for cancer surgery from the literature sources.

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>Surgical margin</th>
<th>Authors</th>
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<tbody>
<tr>
<td>Esophagus</td>
<td>0.1 cm</td>
<td>Chan et al11</td>
</tr>
<tr>
<td>Gastroesophageal junction</td>
<td>5 cm</td>
<td>Barbour et al16</td>
</tr>
<tr>
<td>Stomach (proximal end)</td>
<td>2–4 cm</td>
<td>Tsujitani et al15</td>
</tr>
<tr>
<td>Colon</td>
<td>3 cm</td>
<td>Shimada et al34</td>
</tr>
<tr>
<td>Rectum</td>
<td>1–2 cm</td>
<td>Bujko et al,10 Moore et al15</td>
</tr>
<tr>
<td>Liver</td>
<td>1–3 mm</td>
<td>Shi et al,27 Ker et al18</td>
</tr>
<tr>
<td>HCC</td>
<td>1 cm</td>
<td>Salloum and Castaing29</td>
</tr>
<tr>
<td>CCC</td>
<td>2 cm</td>
<td>Hou et al,26 Konopke et al13</td>
</tr>
<tr>
<td>CLM</td>
<td>3 mm</td>
<td>HCC = hepatocellular carcinoma; CLM = colorectal cancer metastasis; CCC = cholangiocellular carcinoma</td>
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performing an oncological surgery in our patients as shown in the Fig. 1. Such a concept may also be applicable to HCC, which is characterized by unique pathologic features. Intrahepatic spread mainly occurs by portal venous invasion, which is completely different from the invasion of tumors into the surrounding tissues. Multicentric recurrence is common in HCC and could occur anywhere in the liver remnant. The relation between the resection margin and the pattern of recurrence shows that in both the narrow and wide margin groups, most recurrences occurred in the liver remnant at a distal segment or multiple segments, indicating an origin from either intrahepatic metastasis or multicentric carcinogenesis. The margin width did not have prognostic significance in relation to the underlying liver cirrhotic status or the extent of resection. This has an important implication for avoiding extensive resection of HCC associated with cirrhosis. Without question, a positive histological margin is associated with a higher incidence of postoperative recurrence, but a postoperative recurrence could be related to the underlying venous invasion or microsatellites rather than the resection margin. Most intrahepatic recurrences were considered to arise from intrahepatic metastasis by venous dissemination, which a wide resection margin could not prevent. Although surgeons would prefer to have a wide margin to achieve a better prognosis, various factors exist based on the path of carcinogenesis.

Although the prognosis of resected esophageal cancer has improved over the last decade, long-term survival remains poor. A large-scale study on the CRM involvement was performed by Dexter et al. who analyzed a cohort of 135 potentially curative esophagectomies. They demonstrated that CRM involvement was a significant adverse predictor of survival and an independent prognostic variable. By contrast, Hulscher et al. suggested that CRM involvement was not an independent prognostic predictor, but the surgical technique is itself a determinant of disease recurrence. However, the TNM stage will affect the results of CRM involvement. In addition, it should be noted that routine neoadjuvant chemotherapy has become the standard treatment for surgically resectable esophageal cancer. Sujendran et al. examined a cohort of 242 patients who underwent esophagectomy, in which approximately 60% or more had neoadjuvant chemotherapy. They had mentioned that CRM involvement was an independent adverse prognostic factor in patients who had surgery alone as well as in those who underwent preoperative chemotherapy followed by surgery. The study reported that the improvement in survival in patients who underwent preoperative chemotherapy as compared with surgery alone could be attributed to a decrease in the rate of CRM positivity in the neoadjuvant group. Nonetheless, there is accumulating evidence that CRM involvement in the era of routine preoperative chemotherapy is an important prognostic factor following esophagectomy for cancer.

The principles of surgical treatment for primary and secondary liver tumor were different. The general concept of a safety margin is 1 cm in HCC surgery. Ueno et al. performed a retrospective cohort study in 116 consecutive patients who underwent curative hepatic resection for HCCs, and the results indicated that the anatomic resection was more prominent in the group with the nonboundary-type nodules (single nodular type with extranodal growth, confluent multinodular type, and invasive type) than in the group with the boundary type (vaguely nodular and single nodular type). Micrometastases in the nonboundary type were found further from the main tumor (9.5 ± 6.2 mm) than those in the boundary type (within 3.1 ± 1.4 mm). Therefore, in patients with HCC nodules ≥3 cm and with the nonboundary type, the anatomic resection should be performed, because this procedure would be more favorable than the nonanatomic resection in eradicating micrometastases that have extended away from the tumor’s margin. This is the reason why anatomic resection was encouraged to have safety margin in primary liver tumor if liver function allows.

Concerning the metastatic liver tumor from colorectal cancer, margin status remains an important determinant of survival after surgical resection. Andreou et al. reported on the impact of surgical margin status on the overall survival in 378 patients undergoing hepatectomy for colorectal liver metastases after modern preoperative chemotherapy. The survival benefit associated with negative margins (R0 vs. R1 resection) was greater in patients with suboptimal morphologic response (5-year overall survival rate: 62% vs. 11%; p = 0.007). Therefore, they suggested that negative margins remain an important determinant of survival in the era of modern chemotherapy, and should be the primary goal of surgical therapy. The role of positive margins is most pronounced in patients with response to systemic therapy. Because the liver parenchyma is destroyed by the use of surgical equipment such as ultrasonic dissectors, which aspirates a portion of liver parenchyma, or while performing microwave ablation between the tumor and normal liver, it is difficult to increase the true margin. An approximate margin from 1 mm to 1 cm due to transection debridement would not be unreasonable. Hence, even having 1 mm as the cut-off point for a microscopically clear margin was reported previously and some were not in the metastatic liver tumor resection. The part of liver parenchyma destroyed during the dissection and pathological examination just based on a thin slice of tissue will provide

![Figure 1](image_url)  
**Figure 1** Foci of liver cancer cells (arrow) founded with a skip distance from the main tumor (T; alpha feto-protein stain, magnification = 100×).
data on the length of surgical margin, which can be then used as a reference, especially in cases involving false-negative results. Therefore, the results of previous studies on surgical margins and surgical outcomes were quite different and controversial.

Malignant tumors in solid and bowel organs were different with regard to tumor spreading or in tumorigenesis. Distal bowel intramural spread is present within 1 cm distally from the visible tumor in a substantial proportion of patients. For these reasons, for patients with low-lying cancer who are undergoing anterior resection, ≥1 cm of distal bowel clearance is recommended as minimally acceptable. The 1-cm rule is occasionally violated, especially after preoperative radiation or chemoradiotherapy may lead to tumor regression, facilitating complete tumor resection with a <1-cm bowel margin in patients who are otherwise candidates for abdominoperineal resection. Surgeons should understand the true margin while performing dissection and these results will yield a different outcome as well. The adequacy of the distal margin is dependent on both the risk for intramural tumor spread and the distal mesorectal lymphatic spread in addition to the length of surgical margin for patients of rectal cancer. Tumor cells deposited within the mesorectal lymph nodes have been located up to 5 cm distal to the inferior aspect of the tumor, which emphasize the need to adhere to the concept of tumor-specific mesorectal excision (5 cm distal to the inferior border of the tumor) for more proximal rectal cancers. However, for patients with low-lying tumors treated with total mesorectal excision, the primary concern in the absence of lateral or inguinal lymphatic metastases is distal intramural spread. Therefore, Bujko et al had performed a systematic review and proved that distal rectal margins approximately <1 cm did not affect oncologic outcomes after sphincter-preserving surgery for rectal cancer. It is variable to have a close distal margin and rectal cancer recurrence after sphincter-preserving rectal resection. Negative surgical margins are important for local recurrence of rectal cancer treated with sphincter-preserving surgery. However, the association of rectal cancer recurrence with close distal margin is not well established. In the report by Nash et al, pelvic recurrence, other than isolated mucosal recurrence, and lymphovascular invasion were frequently found after the rectal cancer was treated with sphincter-preserving surgery. Hence, the distal margin being a variable was associated with overall recurrence. In general, close distal resection margin identifies patients with an increased risk of mucosal and overall cancer recurrence. Although neither causality of tumorigenesis nor a minimally acceptable margin length can be defined, an analysis of existing data usually supports the importance of achieving a clear distal resection margin in the surgical management of rectal cancer.

In conclusion, the dream of a safe surgical margin for gastroenterological surgery has been realized, but the reality is that it is not completely safe owing to the limited scientific evidence that exists in this regard. A wide resection margin will facilitate less recurrence, theoretically, if the recurrence is at a resection margin. Most recurrent tumors did not occur at the margin site due to the different type of carcinogenesis. A surgeon should try to have a safe margin and try to ablate the tumor completely.

References


