
Surgical Treatment for Digestive Cancer in Japan

Guest Editor
M. Kaminishi, Tokyo

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Surgical Treatment for Esophageal Cancer

Current Issues

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Esophageal cancer · Neoadjuvant therapy · Salvage treatment · Chemoradiotherapy · Minimally invasive surgery

Abstract

Esophageal cancer is one of the most difficult malignancies to cure. The prognosis remains unsatisfactory despite significant advances in surgical techniques and perioperative management. The optimal treatment strategy for localized esophageal cancer has not yet been established. Surgical resection remains the mainstay of treatment for esophageal cancer, and curative resection is the most important surgery. Extended esophagectomy with three-field lymphadenectomy provides the highest quality of tumor clearance and prolongation of patient survival. There has been intense effort in developing novel strategies to treat patients with resectable esophageal cancer. Various combined-modality approaches have been attempted to improve treatment outcomes. Definitive chemoradiotherapy has an impact on long-term survival in patients with resectable esophageal cancer. Accordingly, there are three main combined-modality approaches: esophagectomy with adjuvant chemotherapy or chemoradiotherapy; primary definitive chemoradiotherapy with or without salvage esophagectomy, and preoperative chemoradiotherapy followed by planned

esophagectomy. Recently, owing to the remarkable advances in optical technology, minimally invasive esophagectomy using endoscopic instruments has been introduced into esophageal cancer surgery. This article reviews recent changes in the treatment of esophageal cancer surgery, and considers the role of esophagectomy.

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Introduction

Esophageal cancer is one of the least studied and deadliest cancers worldwide. During the last three decades, important changes have occurred in the epidemiologic patterns of this disease. The most striking has been the dramatic rise in the West of the incidence of adenocarcinoma of the lower esophagus and cardia, which has surpassed squamous cell cancer as the predominant cell type [1–3]. In Asia, however, diagnosed esophageal cancers are predominantly squamous cell in type and are mostly located in the middle third of the esophagus. There has not been a noticeable rise in the incidence of adenocarcinoma of the esophagus and gastric cardia in published Asian data. Recent advances in the diagnosis, staging, and treatment of this neoplastic condition have led to small but significant improvements in survival.

Esophageal cancer is one of the most difficult malignancies to cure [4]; the prognosis remains unsatisfactory despite significant advances in surgical techniques and perioperative management [5]. The optimal management of esophageal cancer remains controversial. While surgery is the mainstay of treatment, the incorporation of chemotherapy and/or radiotherapy suggests that a combined-modality approach is worthy of further investigation. Recently, owing to remarkable advances in optical technology, minimally invasive esophagectomy using endoscopic instruments has been introduced into esophageal cancer surgery. Furthermore, definitive chemoradiotherapy has an impact on long-term survival in patients with resectable esophageal cancer. Salvage esophagectomy is undertaken for recurrence or residual tumor after definitive chemoradiotherapy.

This article reviews the recent changes in the treatment of esophageal cancer surgery, and considers the role of esophagectomy.

Esophageal Resection

Esophageal cancer is a challenging disease that often has a poor outcome. Esophagectomy followed by reconstruction surgery has been the most reliable modality for cure in patients without evidence of disease spread. The three most common techniques for esophagectomy are the transhiatal approach, the Ivor Lewis esophagectomy (right thoracotomy and laparotomy), and the McKeown technique (right thoracotomy followed by laparotomy and neck incision with cervical anastomosis) [4]. There have been several small, underpowered randomized trials comparing transhiatal esophagectomy with standard transthoracic esophagectomy, but none have shown important differences between the two approaches [6, 7]. In a meta-analysis by Hulscher et al. [8], the 5-year survival was approximately 20% after both transthoracic and transhiatal resection, though transthoracic resection was associated with significantly higher early morbidity and mortality. In contrast, Hagen et al. [9] demonstrated significantly better survival (41 vs. 14%; $p < 0.001$) in 30 patients who underwent en bloc esophagectomy compared with 39 patients who underwent transhiatal esophagectomy. They claimed the superiority of extended en bloc esophagectomy over transhiatal resection for carcinoma of the lower esophagus and cardia. There have been three randomized clinical trials comparing transthoracic esophagectomy with transhiatal esophagectomy [10–12]. All of these randomized clinical trials failed to detect any

Table 1. Comparative studies between two-field and three-field lymphadenectomy

| Reference | Procedure | Number of patients | Tumor histology | 5-year OS, % | Survival difference |
|---------------------|-----------|--------------------|-----------------|--------------|---------------------|
| Kato et al. [13] | TTE (3F) | 77 | SC | 49 | $p < 0.01$ |
| | TTE (2F) | 73 | SC | 34 | |
| Isono et al. [15] | TTE (3F) | 1,740 | SC | 34 | $p < 0.001$ |
| | TTE (2F) | 2,671 | SC | 27 | |
| Akiyama et al. [14] | TTE (3F) | 261 | SC | 55 | $p < 0.01$ |
| | TTE (2F) | 283 | SC | 38 | |
| Fujita et al. [16] | TTE (3F) | 63 | SC | 40 | NS |
| | TTE (2F) | 65 | SC | 36 | |

TTE = Transthoracic esophagectomy; 3F = three-field; 2F = two-field; SC = squamous cell carcinoma; NS = not significant; OS = overall survival.

significant differences in patient survival between the two procedures. The randomized study by Hulscher et al. [12] compared 106 patients who underwent transhiatal esophagectomy and 114 who underwent transthoracic esophagectomy for adenocarcinoma of the esophagus and cardia. Transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en bloc lymphadenectomy. Although median overall, disease-free, and quality-adjusted survival did not differ statistically between the groups, there was a trend toward improved long-term survival at 5 years with the extended transthoracic approach.

Most of the data on more aggressive surgery are coming from Asia, in particular from Japan. The 5-year survival after esophagectomy with three-field lymph node dissection was reported to be 48.7% by Kato et al. [13] and 55.0% by Akiyama et al. [14] (table 1). Kato et al. [13] compared two-field with three-field lymphadenectomy for squamous cell carcinoma of the esophagus. The 5-year survival was 48.7% in three-field lymphadenectomy and 33.7% in two-field lymphadenectomy. A major criticism of this study, however, was the difference in patient characteristics. In a nationwide study reported by Isono et al. [15], patient survival was significantly better after three-field lymphadenectomy than after conventional two-field lymphadenectomy. Likewise, Fujita et al. [16] reported the survival of patients undergoing three-field lymphadenectomy to be significantly better than that with two-field lymphadenectomy ($p < 0.05$) in patients with carcinoma in the upper thoracic or mid-thoracic

esophagus with metastasis in the lymph nodes. However, the mortality, morbidity, and postoperative quality of life did not differ between the two procedures [16]. Approximately 80 lymph nodes or more are commonly removed and the reported 5-year survival rates are 40–60% after this procedure [17–21]. Tabira et al. [22] concluded that three-field dissection should be indicated for patients with metastases in 1–4 lymph nodes. Shiozaki et al. [23] reported that cervical lymphadenectomy could be omitted for patients with cancer in the middle or lower thoracic esophagus when no metastasis was found in the recurrent nerve nodes. The efficacy of three-field lymphadenectomy for improving the survival of patients with esophageal cancer has also been demonstrated by Lerut et al. [24] and Altorki et al. [25]. Many Japanese studies have subsequently reported a benefit of three-field lymphadenectomy [26–29].

Minimally Invasive Surgery

Transthoracic surgery for esophageal cancer is associated with a high incidence of pulmonary complications. The recent development of minimally invasive esophagectomy using a thoracoscopic approach may have the potential to minimize morbidity and mortality. One strategy to reduce surgical invasiveness is to perform radical esophagectomy via thoracoscopy rather than as an open procedure. In 1992, Cuschieri et al. [30] described their initial experience with a small series of patients with esophageal cancer in whom resection of the esophagus and mediastinal lymphadenectomy were performed through a right thoracoscopic approach. Since then, the results of thoracoscopic esophagectomy have been reported by a number of centers. Many have described the feasibility of the technique, and a few have reported an advantage over open surgery. However, initial results with the thoracoscopic approach did not show a real benefit over the open approach, in particular due to a high number of pulmonary complications [31–37].

Despite these reports of there being no real advantages to the thoracoscopic approach for esophageal resection, Japanese centers gave it a new impetus. In 1996, Akaishi et al. [38] performed en bloc total esophagectomy with radical lymphadenectomy by right thoracoscopy in 39 patients with esophageal cancer, with the rest of the operation carried out by conventional means. The operating time was 200 ± 41 min, blood loss was 270 ± 157 ml, and 19.7 ± 11 lymph nodes were harvested. No deaths occurred, and 22 of the 39 patients showed only a slight

decrease in their vital capacity and did not require postoperative respiratory support. That the decline in pulmonary function was significantly less than in the open technique was an important result of this study [38]. Kawahara et al. [39] achieved similar results in their series of 23 patients. Osugi et al. [40] described their experience with three-field lymphadenectomy. They compared 77 patients with squamous cell cancer approached by mini-thoracotomy with a control group of 72 patients approached conventionally in a three-stage procedure. Their results in terms of retrieved lymph nodes (33 vs. 32), longer thoracic operation time (227 vs. 186 min), less vital capacity reduction (15 vs. 22%, $p = 0.016$), and similar 3- and 5-year survival rates (70 and 55 vs. 60 and 57%, respectively) were remarkable. They clarified that thoracoscopic resection achieved results comparable to those of open radical esophagectomy, with less surgical trauma [40]. By comparing the outcomes of the first 34 patients operated on with the last 46, this same Japanese group showed the importance of the learning curve in reducing operation time and achieving better outcomes with this approach. They found that the incidence of pulmonary complications with experience of the procedure was only 5%. The last group showed significant reductions in blood loss, duration of thoracoscopy, and incidence of postoperative respiratory complications, and a greater number of retrieved lymph nodes [41]. The estimated risks in thoracoscopic resection appeared to be less after the first 20 cases. These results were confirmed by Taguchi et al. [42] and Smithers et al. [43] in Australia. They compared the results of spirometry and exercise tolerance between patients esophagectomized thoracoscopically and conventionally. Luketich et al. [44] reported an incidence of pneumonia of 7.7% in their study of 222 patients. They described their recent experience with these patients, most of whom underwent esophageal resection with thoracoscopy and laparoscopy. The most important contribution was that the median intensive care unit stay was 1 day and the total hospital stay was just 7 days, with an operative mortality of 1.4% [44]. Quality-of-life scores were similar to the preoperative values and population norms. The results of Nguyen et al. [45] with 46 consecutive patients were concordant with those obtained by Luketich et al. [44]. Recent reports have indicated an advantage of the thoracoscopic procedure performed with robotic assistance, but the full role of robot-assisted esophageal resection remains to be better defined [46, 47].

Minimally invasive esophagectomy could be safely performed in selected cases. The overall benefits of tho-

thoracoscopic esophagectomy tend to relate to the number of cases experienced. Thoracoscopic radical esophagectomy could be performed thoracoscopically with beneficial outcomes by experienced surgeons. Because the efficacy improves with the operator's experience, satisfactory outcomes will be obtained only in centers performing a sufficient number of procedures to provide operators with the opportunity to refine the necessary skills. Moreover, these centers teach various surgical techniques to surgeons, and some randomized protocols are being designed to compare not only the short- but also the long-term oncologic outcomes of minimally invasive approaches with those of conventional techniques [48, 49].

Combined-Modality Treatment

Neoadjuvant Chemotherapy

To improve surgical outcome, preoperative chemotherapy has been investigated compared with surgery alone in randomized trials, though the results of these studies are controversial. Three meta-analysis based on these randomized trials have been published [50–52]. There was no difference in survival rate in the meta-analysis in which the end point was 1-year survival in six randomized trials [50]. In contrast, the 2-year survival was increased with preoperative chemotherapy by 4.4% compared with surgery alone in the meta-analysis in which the end point was 2-year survival in seven randomized trials [51]. If this meta-analysis was limited to four recent randomized trials using cisplatin and 5-fluorouracil (5FU) for chemotherapy, it was shown that the 2-year survival rose by 6.3%. However, an improved survival rate with preoperative chemotherapy was not shown in another meta-analysis in which the end point was 2-year survival [52]. The effect of preoperative chemotherapy is unclear at this time.

Neoadjuvant Chemoradiotherapy

Preoperative chemoradiotherapy was undertaken in the latter half of the 1980s in Europe and America. In some randomized trials, it has been verified that preoperative chemoradiotherapy improves the survival rate of esophageal cancer patients. Although comparatively few centers perform preoperative chemoradiotherapy because of the high-quality surgical treatment available in Japan, one randomized trial report has shown that hyperthermochemoradiotherapy was effective in the local control of esophageal cancer [53]. There are five meta-analyses based on five to seven randomized trials comparing

preoperative chemoradiotherapy followed by surgery with surgery alone. The survival rate with preoperative chemoradiotherapy was not improved in the meta-analysis in which the end point was 1- or 2-year survival [50, 51]. In two meta-analyses in which the end point was 3-year survival, preoperative chemoradiotherapy (20–45 Gy) for resectable disease significantly increased the operation-related mortality within 90 days after surgery; however, the rate of local recurrences was decreased and 3-year survival was significantly improved compared with surgery alone [54, 55]. Preoperative chemoradiotherapy decreased the risk of death by 14% in the meta-analysis in which the end point was the hazard ratio of the survival rate curve [56]. In five reports [57–61] of six randomized trials in this meta-analysis, the survival rate of the preoperative chemoradiotherapy group was higher than that of surgery alone, but not significantly so. In the other report, which was directed only toward esophageal adenocarcinoma, the survival rate of the preoperative chemoradiotherapy group was significantly higher than that of surgery alone [62] (table 2). In the randomized trial reported from Australia in 2005, the disease-free survival rate of the preoperative chemoradiotherapy group was significantly higher than that of surgery alone if the population was limited to those with squamous cell carcinoma [63], but the difference according to histological type does not always correspond between reports. Preoperative chemoradiotherapy is a combined therapy that can improve long-term survival after the 3rd year following surgery. However, there are no grounds to recommend preoperative chemoradiotherapy as a preoperative treatment because there is no randomized trial of this modality in Japan.

Adjuvant Chemotherapy

A randomized trial of postoperative chemotherapy in esophageal squamous cell carcinoma was performed by the Japan Clinical Oncology Group (JCOG) in 1992 [64]. This trial compared surgery alone (n = 100) and postoperative chemotherapy groups (n = 122; JCOG9204); the postoperative chemotherapy involved two courses of cisplatin (80 mg/m², day 1) and 5FU (800 mg/m², 5 days). In this study, no significant difference was observed in the survival rate, but a significant difference was observed in the disease-free survival rate (43% in surgery alone arm vs. 58% in postoperative chemotherapy arm) [64]. Furthermore, this study reported that postoperative chemotherapy was especially useful for patients with lymph node metastases. In contrast, the effect of postoperative chemotherapy on survival rate was not significant

Table 2. Randomized trials comparing chemoradiotherapy followed by surgery with surgery alone

| Regimen | Radiation Gy | Number of patients | Resectability, % | Pathologic CR, % | Survival % | p value | Reference |
|---------------------------|--------------|--------------------|------------------|------------------|--------------|---------|----------------------|
| CDDP+5FU Surgery alone | 45 | 50 50 | 94 100 | 28 | 30 16 | NS | Urba et al. [57] |
| CDDP+5FU Surgery alone | 37 | 143 139 | 96.5 98.6 | 26 | 37 35 | NS | Bosset et al. [58] |
| CDDP+5FU Surgery alone | 20 | 41 45 | 85 93 | 10 | 19.2 13.8 | NS | Le Prise et al. [59] |
| CDDP+5FU Surgery alone | 45 | 35 34 | 73.4 100 | – | 26 20 | NS | Apinop et al. [60] |
| CDDP+BLM Surgery alone | 35 | 53 50 | 88.7 82.0 | – | 17 9 | NS | Nygaard et al. [61] |
| CDDP+5FU Surgery alone | 40 | 58 55 | 100 100 | 25 | 32 6 | 0.01 | Walsh et al. [62] |

CDDP = Cisplatin; 5FU = 5-fluorouracil; CR = complete response; NS = not significant.

in a meta-analysis based on randomized trials in Europe and America [50]. There was no evidence that postoperative chemotherapy improved the survival rate after curative resection in esophageal cancer patients. However, the disease-free survival rate was significantly improved by postoperative chemotherapy in the randomized trial performed in Japan. Therefore, postoperative chemotherapy is thought to be effective in preventing recurrence after surgery.

Adjuvant Radiotherapy

There are four randomized trials comparing surgery alone and postoperative radiotherapy (45–65 Gy) [65–68]. These reports showed no significant improvement in survival rate, though the local recurrence rate in the irradiated area was decreased by postoperative radiotherapy. In a meta-analysis based on these randomized trials, no significant improvement in survival rate with postoperative radiotherapy was observed. Therefore, postoperative radiotherapy is not considered a standard treatment [50].

Salvage Esophagectomy

Definitive chemoradiotherapy has recently been chosen more often as a first-line therapy for resectable esophageal cancer [69, 70]. However, definitive chemoradio-

therapy does not achieve a complete response (CR) in all esophageal cancers. Furthermore, even if CR has been attained, some tumors recur later [69, 71]. Unfortunately, it is difficult to completely control a lesion with definitive chemoradiotherapy, and 40–60% of patients have persistent or relapsed tumor at the primary site within 1 year [70, 71]. Salvage surgery is often required for these uncontrollable tumors.

Esophagectomy after chemoradiotherapy, whether planned or salvage, causes greater morbidity than primary esophagectomy [58, 72, 73]. Radiation damages mediastinal structures, and causes inflammation early (several weeks) and fibrosis later (several months). Tissue injury depends on the total radiation dose and the method of delivery. High total dose, large treatment fields, and large fractions cause more severe tissue injury [58, 71, 72, 74, 75]. There are also complications of esophagectomy after radiotherapy treatment; esophagogastric anastomotic leaks, adult respiratory distress syndrome, airway complications, and death are the most common [76–79]. Even specialized units report operative mortalities of over 10% for esophagectomy after chemoradiotherapy [77, 79]. Salvage esophagectomy may cause even more morbidity than planned esophagectomy. Swisher et al. [80] described a series of patients treated with planned or salvage esophagectomy at the MD Anderson Cancer Center. Salvage esophagectomy patients had a significantly higher incidence of anastomotic leaks (39

vs. 7%; $p = 0.005$) and longer hospital stay (29 vs. 18 days; $p = 0.03$) than those treated with planned esophagectomy. The operative mortality was also higher (15 vs. 6%; $p = 0.20$), but this did not reach statistical significance [80].

Because salvage esophagectomy carries a high risk, it should be performed only in selected patients who are likely to benefit, namely those with isolated persistent or recurrent local malignant disease. Therefore, patients with systemic lymph node metastases must be excluded. Patients who meet the oncologic criteria for salvage esophagectomy need careful assessment of their fitness for surgery [81]. Chronic lung disease, poor performance status, and malnutrition are predictors of complications after standard esophagectomy [82–85]. Nakamura et al. [86] have said that vital capacity and albumin level in particular are important risk factors for complications after transthoracic esophagectomy [85, 87].

For persistence or recurrence after chemoradiotherapy, salvage surgery is important but carries a high risk. We must, therefore, consider adaptation carefully.

Conclusion

Esophageal cancer is one of the most difficult malignancies to cure. The optimal treatment strategy for localized esophageal cancer has not yet been established. Surgical resection remains the mainstay of treatment for esophageal cancer, and there has been intense effort to develop novel strategies for the treatment of patients with resectable esophageal cancer. Various combined-modality approaches have been attempted to improve treatment outcomes. There are three main combined-modality approaches: esophagectomy with adjuvant chemotherapy or chemoradiotherapy; primary definitive chemoradiotherapy with or without salvage esophagectomy, and preoperative chemoradiotherapy followed by planned esophagectomy. Furthermore, owing to the remarkable advances in optical technology, minimally invasive esophagectomy using endoscopic instruments has been introduced to esophageal cancer surgery. This article is a review of the recent changes in the treatment of esophageal cancer surgery, and considers the role of esophagectomy.

References

- 1 Law S, Wong J: Current management of esophageal cancer. *J Gastrointest Surg* 2005; 9:291–310.
- 2 Devesa SS, Blot WJ, Fraumeni JF Jr: Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049–2053.
- 3 Kuwano H, Kato H, Miyazaki T, Fukuchi M, Masuda N, Nakajima M, Fukai Y, Sohda M, Kimura H, Faried A: Genetic alterations in esophageal cancer. *Surg Today* 2005;35:7–18.
- 4 Wright CD: Esophageal cancer surgery in 2005. *Minerva Chir* 2005;60:431–444.
- 5 Enzinger PC, Mayer RJ: Esophageal cancer. *N Engl J Med* 2003;349:2241–2252.
- 6 Pommier RF, Vetto JT, Ferris BL, Wilmarth TJ: Relationships between operative approaches and outcomes in esophageal cancer. *Am J Surg* 1998;175:422–425.
- 7 Rentz J, Bull D, Harpole D, et al: Transthoracic versus transhiatal esophagectomy: a prospective study of 945 patients. *J Thorac Cardiovasc Surg* 2003;125:1114–1120.
- 8 Hulscher JBF, Tijssen JGP, Obertop H, van Lanschot JJB: Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg* 2001;72:306–313.
- 9 Hagen JA, Peters JH, DeMeester TR: Superiority of extended en bloc esophagogastrectomy for carcinoma of the lower esophagus and cardia. *J Thorac Cardiovasc Surg* 1993; 106:850–858.
- 10 Goldminc M, Maddern G, Le Prise E, Meunier B, Campion JP, Launois B: Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. *Br J Surg* 1993;80:367–370.
- 11 Chu KM, Law SY, Fok M, Wong J: A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. *Am J Surg* 1997;174:320–324.
- 12 Hulscher JBF, van Sandick JW, Boer AGEM, et al: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662–1669.
- 13 Kato H, Watanabe H, Tachimori Y, Iizuka T: Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. *Ann Thorac Surg* 1991;51:931–935.
- 14 Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y: Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994;220:364–373.
- 15 Isono K, Sato H, Nakayama K: Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. *Oncology* 1991;48:411–420.
- 16 Fujita H, Kakegawa T, Yamana H, et al: Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. *Ann Surg* 1995;222:654–662.
- 17 Baba M, Aikou T, Yoshinaka H, et al: Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. *Ann Surg* 1994; 219:310–316.
- 18 Matsubara T, Ueda M, Nagao N, Takahashi T, Nakajima T, Nishi M: Cervicothoracic approach for total mesoesophageal dissection in cancer of the thoracic esophagus. *J Am Coll Surg* 1998;187:238–245.
- 19 Nishimaki T, Suzuki T, Suzuki S, Kuwabara S, Hatakeyama K: Outcomes of extended radical esophagectomy for thoracic esophageal cancer. *J Am Coll Surg* 1998;186:306–312.
- 20 Nishihira T, Hirayama K, Mori S: A prospective randomized trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus. *Am J Surg* 1998;175:47–51.
- 21 Watanabe H, Kato H, Tachimori Y: Significance of extended systemic lymph node dissection for thoracic esophageal carcinoma in Japan. *Recent Results Cancer Res* 2000;155: 123–133.

- 22 Tabira Y, Kitamura N, Yoshioka M, Tanaka M, Nakano K, Toyota N, Mori T: Significance of three-field lymphadenectomy for carcinoma of the thoracic esophagus based on depth of tumor infiltration, lymph nodal involvement and survival rate. *J Cardiovasc Surg (Torino)* 1999;40:737-740.
- 23 Shiozaki H, Yano M, Tsujinaka T, Inoue M, Tamura S, Doki Y, Yasuda T, Fujiwara Y, Monden M: Lymph node metastasis along the recurrent nerve chain is an indication for cervical lymph node dissection in thoracic esophageal cancer. *Dis Esophagus* 2001;14:191-196.
- 24 Lerut T, Naftoux P, Moons J, Coosemans W, Decker G, De Leyn P, Van Raemdonck D, Ectors N: Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg* 2004;240:962-972.
- 25 Altorki N, Kent M, Ferrara C, Port J: Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. *Ann Surg* 2002;236:177-183.
- 26 Udagawa H, Akiyama H: Surgical treatment of esophageal cancer: Tokyo experience of the three-field technique. *Dis Esophagus* 2001;14:110-114.
- 27 Shimada H, Okazumi S, Matsubara H, Nabeya Y, Shiratori T, Shimizu T, Shuto K, Hayashi H, Ochiai T: Impact of the number and extent of positive lymph nodes in 200 patients with thoracic esophageal squamous cell carcinoma after three-field lymph node dissection. *World J Surg* 2006;30:1441-1449.
- 28 Fujita H, Sueyoshi S, Tanaka T, Fujii T, Toh U, Mine T, Sasahara H, Sudo T, Matono S, Yamana H, Shirouzu K: Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: comparing the short- and long-term outcome among the four types of lymphadenectomy. *World J Surg* 2003;27:571-579.
- 29 Tachibana M, Kinugasa S, Yoshimura H, Shibakita M, Tonomoto Y, Dhar DK, Nagasue N: Clinical outcomes of extended esophagectomy with three-field lymph node dissection for esophageal squamous cell carcinoma. *Am J Surg* 2005;189:98-109.
- 30 Cuschieri A, Shimi S, Banting S: Endoscopic oesophagectomy through a right thoracoscopic approach. *J R Coll Surg Edinb* 1992;37:7-11.
- 31 Azagra JS, Ceuterick M, Goergen M, et al: Thoracoscopy in oesophagectomy for oesophageal cancer. *Br J Surg* 1993;80:320-321.
- 32 Gossot D, Fourquier P, Celerier M: Thoracoscopic esophagectomy: technique and initial results. *Ann Thorac Surg* 1993;56:667-670.
- 33 Collard JM, Lengele B, Otte JB, Kestens PJ: En bloc and standard esophagectomies by thoracoscopy. *Ann Thorac Surg* 1993;56:675-679.
- 34 McAnena OJ, Rogers J, Williams NS: Right thoracoscopically assisted oesophagectomy for cancer. *Br J Surg* 1994;81:236-238.
- 35 Dexter SP, Martin IG, McMahon MJ: Radical thoracoscopic esophagectomy for cancer. *Surg Endosc* 1996;10:1113-1115.
- 36 Robertson GS, Lloyd DM, Wicks AC, Veitch PS: No obvious advantages for thoracoscopic two-stage oesophagectomy. *Br J Surg* 1996;83:675-678.
- 37 Law S, Fok M, Chu KM, Wong J: Thoracoscopic esophagectomy for esophageal cancer. *Surgery* 1997;122:8-14.
- 38 Akaishi T, Kaneda I, Higuchi N, et al: Thoracoscopic en bloc total esophagectomy with radical mediastinal lymphadenectomy. *J Thorac Cardiovasc Surg* 1996;112:1533-1540.
- 39 Kawahara K, Maekawa T, Okabayashi K, et al: Video-assisted thoracoscopic esophagectomy for esophageal cancer. *Surg Endosc* 1999;13:218-223.
- 40 Osugi H, Takemura M, Higashino M, Takada N, Lee S, Kinoshita H: A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. *Br J Surg* 2003;90:108-113.
- 41 Osugi H, Takemura M, Higashino M, et al: Learning curve of video-assisted thoracoscopic esophagectomy and extensive lymphadenectomy for squamous cell cancer of the thoracic esophagus and results. *Surg Endosc* 2003;17:515-519.
- 42 Taguchi S, Osugi H, Higashino M, et al: Comparison of three-field esophagectomy for esophageal cancer incorporating open or thoracoscopic thoracotomy. *Surg Endosc* 2003;17:1445-1450.
- 43 Smithers BM, Gotley DC, McEwan D, Martin I, Bessel J, Doyle L: Thoracoscopic mobilization of the esophagus. A 6 year experience. *Surg Endosc* 2001;15:176-182.
- 44 Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al: Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg* 2003;238:486-494.
- 45 Nguyen NT, Roberts P, Follette DM, Rivers R, Wolfe BM: Thoracoscopic and laparoscopic esophagectomy for benign and malignant disease: lessons learned from 46 consecutive procedures. *J Am Coll Surg* 2003;197:902-913.
- 46 Horgan S, Berger RA, Elli EF, Espot NJ: Robotic-assisted minimally invasive transhiatal esophagectomy. *Am Surg* 2003;69:624-626.
- 47 Bodner JC, Zitt M, Ott H, et al: Robotic-assisted thoracoscopic surgery (RATS) for benign and malignant esophageal tumors. *Ann Thorac Surg* 2005;80:1202-1206.
- 48 Pierre AF, Luketich JD: Technique and role of minimally invasive esophagectomy for premalignant and malignant diseases of the esophagus. *Surg Oncol Clin North Am* 2002;11:337-350.
- 49 Cuesta MA, van den Broek WT, van der Peet DL, Meijer S: Minimally invasive esophageal resection. *Semin Laparosc Surg* 2004;11:147-160.
- 50 Malthaner RA, Wong RK, Rumble RB, Zuraw L: Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a systematic review and meta-analysis. *BMC Med* 2004;2:35.
- 51 Kaklamanos IG, Walker GR, Ferry K, Franceschi D, Livingstone AS: Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 2003;10:754-761.
- 52 Urschel JD, Vasan H, Blewett CJ: A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2002;183:274-279.
- 53 Sugimachi K, Kitamura K, Baba K, Ikebe M, Morita M, Matsuda H, Kuwano H: Hyperthermia combined with chemotherapy and irradiation for patients with carcinoma of the oesophagus - a prospective randomized trial. *Int J Hyperthermia* 1992;8:289-295.
- 54 Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, Falchi AM, Craxi A, Camma C: Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut* 2004;53:925-930.
- 55 Urschel JD, Vasan H: A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2003;185:538-543.
- 56 Greer SE, Goodney PP, Sutton JE, Birkmeyer JD: Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. *Surgery* 2005;137:172-177.
- 57 Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;19:305-313.
- 58 Bosset JF, Gignoux M, Triboulet JP, Tiret E, Manton G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T: Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. *N Engl J Med* 1997;337:161-167.
- 59 Le Prise E, Etienne PL, Meunier B, Maddern G, Ben Hassel M, Gedouin D, Boutin D, Campion JP, Launois B: A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994;73:1779-1784.

- 60 Apinop C, Puttisak P, Preecha N: A prospective study of combined therapy in esophageal cancer. *Hepatogastroenterology* 1994;41:391-393.
- 61 Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, Mantyla M, Modig H, Munck-Wikland E, Rosengren B, et al: Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Surg* 1992;16:1104-1110.
- 62 Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996;335:462-467.
- 63 Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET, Denham JW: Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005;6:659-668.
- 64 Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, Takiyama W, Watanabe H, Isono K, Aoyama N, Makuuchi H, Tanaka O, Yamana H, Ikeuchi S, Kabuto T, Nagai K, Shimada Y, Kinjo Y, Fukuda H: Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study - JCOG9204. *J Clin Oncol* 2003;21:4592-4596.
- 65 Teniere P, Hay JM, Fingerhut A, Fagniez PL: Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. *French University Association for Surgical Research. Surg Gynecol Obstet* 1991;173:123-130.
- 66 Fok M, Sham JS, Choy D, Cheng SW, Wong J: Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. *Surgery* 1993;113:138-147.
- 67 Zieren HU, Muller JM, Jacobi CA, Pichlmaier H, Muller RP, Staar S: Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. *World J Surg* 1995;19:444-449.
- 68 Xiao ZF, Yang ZY, Liang J, Miao YJ, Wang M, Yin WB, Gu XZ, Zhang de C, Zhang RG, Wang LJ: Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. *Ann Thorac Surg* 2003;75:331-336.
- 69 Hironaka S, Ohtsu A, Boku N, Muto M, Nagashima F, Saito H, Yoshida S, Nishimura M, Haruno M, Ishikura S, Ogino T, Yamamoto S, Ochiai A: Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2-3)N(any)M(0) squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003;57:425-433.
- 70 Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV, Leichman LL: Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623-1627.
- 71 Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Daivis L, Emami B: Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326:1593-1598.
- 72 Geh JI, Crellin AM, Glynne-Jones R: Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer. *Br J Surg* 2001;88:338-356.
- 73 Adelstein DJ, Rice TW, Becker M, Larto MA, Kirby TJ, Koda A, Tefft M, Zuccaro G: Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. *Cancer* 1997;80:1011-1020.
- 74 Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP: INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: highdose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167-1174.
- 75 Urba S G, Orringer M B, Perez-Tamayo C, Bromberg J, Forastiere A: Concurrent preoperative chemotherapy and radiation therapy in localized esophageal adenocarcinoma. *Cancer* 1992;69:285-291.
- 76 Stahl M, Wilke H, Fink U, Stuschke M, Walz MK, Siewert JR, Molls M, Fett W, Makoski HB, Breuer N, Schmidt U, Niebel W, Sack H, Eigler FW, Seeber S: Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer. Interim analysis of a phase II trial. *J Clin Oncol* 1996;14:829-837.
- 77 Chidel MA, Rice TW, Adelstein DJ, Kupelian PA, Suh JH, Becker M: Resectable esophageal carcinoma: local control with neoadjuvant chemotherapy and radiation therapy. *Radiology* 1999;213:67-72.
- 78 Bartels HE, Stein HJ, Siewert JR: Tracheobronchial lesions following oesophagectomy: prevalence, predisposing factors and outcome. *Br J Surg* 1998;85:403-406.
- 79 Keller SM, Ryan LM, Coia LR, Dang P, Vaught DJ, Diggs C, Weiner LM, Benson AB: High dose chemoradiotherapy followed by esophagectomy for adenocarcinoma of the esophagus and gastroesophageal junction: results of a phase II study of the Eastern Cooperative Oncology Group. *Cancer* 1998;83:1908-1916.
- 80 Swisher SG, Wynn P, Putnam JB, Mosheim MB, Correa AM, Komaki RR, Ajani JA, Smythe WR, Vaporciyan AA, Roth JA, Walsh GL: Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg* 2002;123:175-183.
- 81 Urschel JD, Sellke FW: Complications of salvage esophagectomy. *Med Sci Monit* 2003;9:RA173-RA180.
- 82 Ferguson MK, Durkin AE: Preoperative prediction of the risk of pulmonary complications after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2002;123:661-669.
- 83 Tabira Y, Okuma T, Kondo K, Yoshioka M, Mori T, Tanaka M, Nakano K, Kitamura N: Does neoadjuvant chemotherapy for carcinoma in the thoracic esophagus increase postoperative morbidity? *Jpn J Thorac Cardiovasc Surg* 1999;47:361-367.
- 84 Stein HJ, Brucher BL, Sandler A, Siewert JR: Esophageal cancer: patient evaluation and pretreatment staging. *Surg Oncol* 2001;10:103-111.
- 85 Nagawa H, Kobori O, Muto T: Prediction of pulmonary complications after transthoracic oesophagectomy. *Br J Surg* 1994;81:860-862.
- 86 Nakamura T, Hayashi K, Ota M, Eguchi R, Ide H, Takasaki K, Mitsuhashi N: Salvage esophagectomy after definitive chemotherapy and radiotherapy for advanced esophageal cancer. *Am J Surg* 2004;188:261-266.
- 87 Law SY, Fok M, Wong J: Risk analysis of squamous cell carcinoma of the esophagus. *World J Surg* 1994;18:339-346.

Surgical Treatment of Early Gastric Cancer

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Key Words

Gastric cancer · Endoscopy · Ultrasound, endoscopic

Abstract

Around half the cases of gastric cancer are found in the early stage in Japan. With an expected good prognosis, many treatment options have been developed to maintain a good quality of life of the patients after the treatment. Gastric cancer is diagnosed with endoscopy, and the depth of invasion is diagnosed with endoscopy and endoscopic ultrasound. One of the new treatments is endoscopic submucosal dissection. Improvements in surgical treatment are minimizing lymph node dissection, reconstruction methods, laparoscopy-assisted surgery, and sentinel node navigation surgery. Minimizing lymph node dissection for early gastric cancer is well described in the Guidelines for Gastric Cancer Treatments. Pylorus-preserving gastrectomy, jejunal interposition, pouch reconstruction, and Roux-en-Y reconstruction after distal gastrectomy are improvements in reconstruction after gastrectomy. More and more surgeons start laparoscopy-assisted gastrectomy with lymph node dissection. Even with these improvements, the 5-year survival of early gastric cancer is more than 90% in Japan. Further improvements would be possible in the future.

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Introduction

The definition of early gastric cancer is tumor confined to the mucosal layer or the mucosal and submucosal layer, regardless of lymph node status [1]. In Japan around half the gastric cancers are found in early stages [2]. According to this, many treatment options for early gastric cancer have been developed to maintain the patients' quality of life even after treatment. One of the remarkable changes in treatment is the use of endoscopic submucosal dissection. The condition for this treatment is that the tumor can be dissected under endoscopy and that there are no lymph node metastases. To fulfill this condition, accumulated data on resected gastric cancer status without lymph node metastasis were analyzed. The surgery has also been modified for early gastric cancer. One of the modifications is the extent of lymph node dissection. Laparoscopy-assisted gastrectomy is also a new technique in the treatment of early gastric cancer.

To apply these treatments correctly, the 1st edition of the Guidelines for Gastric Cancer Treatment was published in 2001 [3] and the 2nd edition was published in 2004 [4]. The guidelines are very useful for the application of standard treatment in clinical settings. They divide the treatment methods into a daily clinical category and a clinical research category, which means that there is potential to improve treatment for gastric cancer. In this article, we will discuss the surgical treatment of early gastric cancer as well as the prognosis of the patients.

Table 1. Age distribution of resected gastric cancer cases

| | Age, years | | | | |
|--------------------|------------|---------------|---------------|-------------|---------------|
| | <39 | 40–59 | 60–79 | >80 | not specified |
| Total number | 302 (3.8%) | 2,805 (35.4%) | 4,276 (53.9%) | 344 (43.4%) | 207 (2.6%) |
| 5-year survival, % | 72.4 | 76.1 | 64.8 | 39.7 | 72.1 |

Epidemiology

In 2002, the mortality rate from gastric cancer was around 40 in 100,000 in Japan. In 1998, the age-adjusted disease rate was 60.4 in 100,000 and the age-adjusted mortality rate was 27.3 in 100,000. Both the age-adjusted disease rate and the age-adjusted mortality rate have gradually decreased. However, without adjustment both rates have not changed due to the increase in higher age groups in the population.

Data on gastric cancers treated in 1991, registered by the Japanese Gastric Cancer Association, were recently published [2]. At that time, endoscopic mucosal dissection was not as common, and most of the tumors were surgically resected with lymph node dissection. The data on 8,851 patients with primary gastric cancer were collected from 113 hospitals, and the data on 7,935 patients could be analyzed. Among the 7,935 cases, 3,871 (48.8%) tumors were in the early stages, including 2,209 (27.8% of tumors, 57.1% of early tumors) mucosal tumors and 1,662 (20.9%, 42.9%) submucosal tumors. 5,493 (69.2%) patients were male and 2,441 (30.8%) female. The age distribution is shown in table 1. The incidence of gastric cancer increases after 40 years of age and is highest in the 60- to 79-year age group. The prognosis of gastric cancer itself does not differ between age groups.

Diagnosis

Health check-up program is in progress for people over 39 years of age in Japan. In an ordinal health check-up, barium-swallow roentgenoscopy or serum pepsinogen are common. However, more and more people are having endoscopy without barium swallow. The reason for this may be that patients with suspected lesions on barium swallow have to have endoscopy, and they want to finish the examination with one method. Another reason may be that many physicians believe endoscopy is more sensitive than barium swallow.

The diagnosis of gastric cancer is made histologically from tissue biopsied under endoscopy. The depth of invasion is diagnosed using endoscopy and endoscopic ultrasonography. Lymph node metastasis is analyzed with computed tomography, ultrasonography, and endoscopic ultrasonography. Distant metastases are also analyzed with computed tomography.

Endoscopic Treatment

Endoscopic treatment for early gastric cancer is a new method which started about 10 years ago. The condition for the treatment is a lack of lymph node metastasis. In daily clinical settings, the guidelines define gastric cancer as being confined to the mucosal layer, <2 cm in diameter, differentiated histological type, and without ulcer scar.

However, endoscopic submucosal dissection, a new technique which enables the resection of larger lesions, is changing the indication. In our institute, endoscopic submucosal dissection is indicated when the tumor remains in the mucosal layer and is of a differentiated histological type. After dissection, if the tumor is found to be invading the submucosal layer or vein, the patient is recommended to receive additional surgery.

Surgical Treatment

Guidelines

The guidelines for early gastric cancer in daily clinical settings and in clinical research are shown in tables 2 and 3 [3, 4]. In fact, N2 or N3 early gastric cancer is rarely diagnosed. A mucosal tumor without lymph node metastases and a submucosal tumor of differentiated histological type, <1.5 cm in diameter without lymph node metastases, can be operated using minimal lymph node dissection D1+ α . A tumor of >2.1 cm in diameter with N1 lymph node metastases and a tumor with N2 lymph node

Table 2. Treatment options by stage for clinical practice

| | N0 (stage IA) | N1 (stage IB) | N2 (stage II) | N3 (stage IV) |
|----------------------|---|--|------------------|--|
| Mucosal cancer T1 | EMR (en bloc resection; differentiated type, ≤ 2.0 cm in diameter; depressed type without ulceration) Modified surgery A (other than those above) | Modified surgery B (≤ 2.0 cm in diameter) Standard surgery (≥ 2.1 cm in diameter) | Standard surgery | Extended surgery, palliative operation, chemotherapy, radiation therapy, palliative care |
| Submucosal cancer T1 | Modified surgery A (differentiated type, ≤ 1.5 cm in diameter) Modified surgery B (other than those above) | Modified surgery B (≤ 2.0 cm in diameter) Standard surgery (≥ 2.1 cm in diameter) | Standard surgery | Extended surgery, palliative operation, chemotherapy, radiation therapy, palliative care |

Modified surgery A and B = resection less than standard surgery including omentum-preserving procedure, omission of omento-bursectomy, pylorus-preserving gastrectomy, and vagus-preserving procedure. According to the extent of lymph node dissection, modified surgery is classified into surgery A (D1+ α dissection) and surgery B (D1+ β dis-

section). Dissected lymph nodes for α : No. 7 regardless of the location of lesions, and additionally No. 8a in cases with lesions located in the lower third of the stomach. Dissected lymph nodes for β : No. 7, 8a and 9.

Standard surgery = Resection of two thirds of the stomach with D2 dissection. EMR = Endoscopic mucosal resection.

Table 3. Treatment options according to stage for clinical study

| | N0 (stage IA) | N1 (stage IB) | N2 (stage II) | N3 (stage IV) |
|-----------------------------|---|----------------------------------|---------------|--|
| Mucosal cancer T1 (>2.0 cm) | EMR (piecemeal resection) ESD (submucosal resection) EMR (laser treatment for incomplete resection) | Laparoscopy-assisted gastrectomy | – | Extended surgery (combined resection, dissection) Reduction surgery Chemotherapy (systemic or regional) Hyperthermochemotherapy |
| Submucosal cancer T1 | Wedge, segmental resection Laparoscopic wedge gastrectomy Laparoscopy-assisted gastrectomy | Laparoscopy-assisted gastrectomy | – | Extended surgery (combined resection, dissection) Reduction surgery Chemotherapy (systemic or regional) Hyperthermochemotherapy |

Extended surgery (dissection) = Extended gastrectomy with extended lymphadenectomy.

Extended surgery (combined resection, dissection) = Gastrectomy with combined resection of involved organs and extended lymphadenectomy.

EMR = Endoscopic mucosal resection; ESD = endoscopic submucosal dissection.

metastases require standard operation. Other early gastric cancers with N0 or N1 can be operated using minimal lymph node dissection D1+ β .

Reconstruction

The form of reconstruction after the resection of the stomach is one of the important issues in the treatment of early gastric cancer because of the good prognosis of the patients. Traditionally, Billroth I and Billroth II are common methods of reconstructions after distal gastrectomy. Many surgeons do not prefer Billroth II because of its bile reflux, remnant gastritis, and the high rate of gastric stump cancer. In place of Billroth II, Roux-en-Y reconstruction is now becoming common for reconstruction after distal gastrectomy. Compared to Billroth I, Roux-en-Y has a low rate of remnant gastritis, gastric

stump cancer, and anastomotic leakage; however, Roux-en-Y has a higher rate of Roux stasis syndrome, gallbladder stone formation, and needs a longer operation time. No comparison of the clinical data in a large volume randomized control study has been made, but the superiority of Roux-en-Y with regard to less bile reflux and less inflammation in the remnant stomach and its inferiority with regard to the long operation time and long hospital stay have been reported [5].

After total gastrectomy, Roux-en-Y reconstruction and jejunal interposition are the common methods. Jejunal interposition makes foods pass through duodenum but the operation technique is more complicated. A preliminary randomized clinical trial was started about 5 years ago, but no difference was detected among the roughly 200 patients between these two methods.

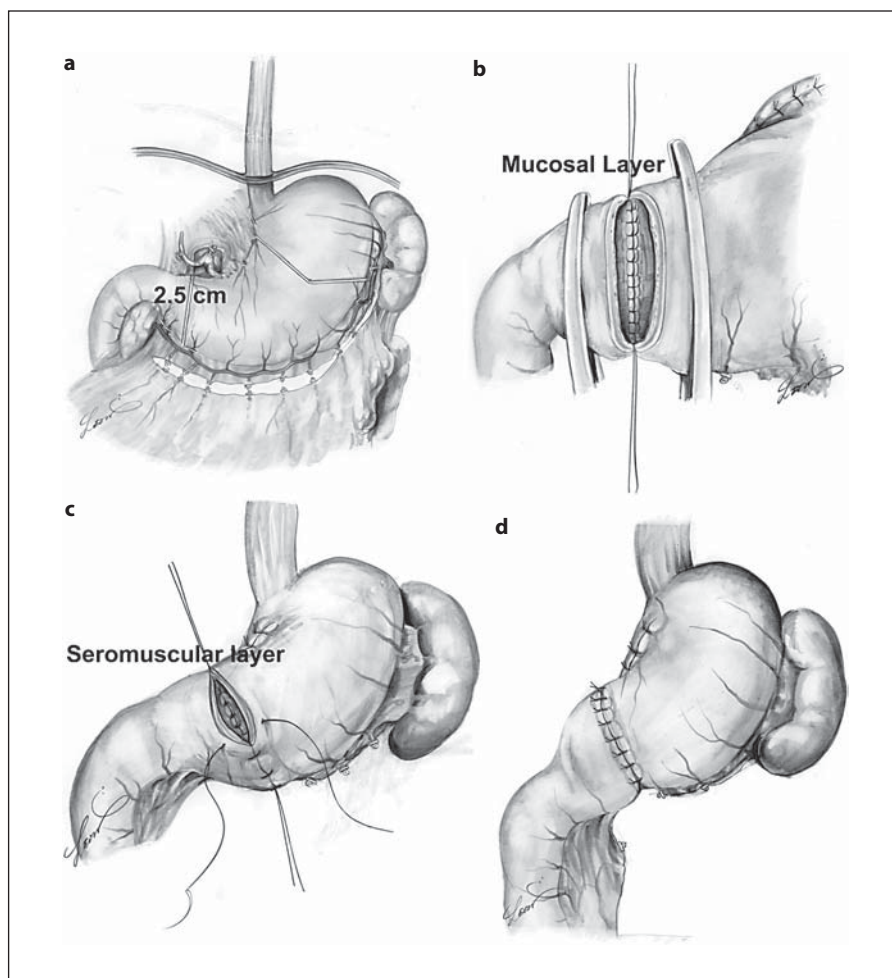


Fig. 1. Schematic illustration of pylorus-preserving gastrectomy (PPG). Anastomosis of PPG. The proximal portion of the stomach is resected with a 75-mm linear cutter. the resection is the same as in conventional distal gastrectomy (a). A two-layer primary gastro-gastro anastomosis is performed; that is, the mucosal layer is sutured continuously with 3-0 absorbable monofilament (b). The seromuscular layer is sutured by a knotting suture with 3-0 Vicryl (c). The stomach is placed back into the abdominal cavity (d), and the closed drain is advanced through the Winslow foramen to the left infrahepatic cavity.

Pouch reconstruction is one of the options for reconstruction after distal gastrectomy, proximal gastrectomy, and total gastrectomy. There are very little data to support pouch reconstruction, and the efficacy of pouch reconstruction has not yet been defined. In our opinion, an evaluation of the quality of life depending on the time course after operation will be needed for the pouch reconstruction [6, 7].

Pylorus-preserving gastrectomy (PPG) following gastro-gastro anastomosis can be included in the reconstruction options. PPG is a modification of distal gastrectomy preserving 2–3 cm of the pyloric cuff which maintains pylorus ring function. The indication of PPG is restricted to tumors with a distance of more than 4.5–5 cm from the pylorus ring to maintain the distal margin (fig. 1) [8, 9]. The incidence of early dumping syndrome is reported to be lower in PPG (8%) than in distal gastrectomy with Billroth I reconstruction (33%) [10].

Laparoscopy-Assisted Surgery

Laparoscopy-assisted gastrectomy with lymph node dissection is now one of the modalities for early gastric cancer surgery [11]. The guidelines also define laparoscopy-assisted surgery as a treatment of clinical stage IB cancer. The quality of laparoscopic surgery is reported not to be worse than conventional open laparotomy surgery, and the surgical invasiveness is reported to be less in laparoscopy-assisted surgery [12, 13]. A new issue in the laparoscopic surgery is the education of younger surgeons.

Sentinel Node Navigation Surgery

Sentinel node navigation surgery is still under trial for gastric cancer. It is still difficult to detect sentinel nodes and dissect lymph nodes in order to analyze the accuracy of the method. Several reports agree that the indication of sentinel node mapping is early cN0 tumors [14, 15].

Table 4. Prognosis and recurrent pattern of resected early gastric cancer

| | Total number | Survival, %, at | | | | | Recurrence | | | |
|-----------|--------------|-----------------|---------|---------|---------|---------|------------|------------|-----------|--------------------|
| | | 1 year | 2 years | 3 years | 4 years | 5 years | local | peritoneal | liver | distant metastases |
| Mucosa | 2,209 | 98.0 | 96.6 | 95.2 | 94.0 | 92.5 | 6 (0.3%) | 4 (0.2%) | 3 (0.1%) | 2 (0.1%) |
| Submucosa | 1,662 | 96.0 | 93.7 | 90.8 | 89.3 | 87.6 | 17 (1.0%) | 14 (0.8%) | 17 (1.0%) | 7 (0.4%) |

The detection rate is reported to be 95%, the false-negative rate of lymph node metastasis is 4%, which is still too high to apply sentinel node navigation surgery without lymph node dissection other than the detected sentinel node. Further improvements are needed.

Prognosis

The Kaplan-Mayer curve is shown in figure 2. The 5-year survival of early gastric cancer is 90.4%. Recurrent pattern is shown in table 4. The 5-year survival of stage IA gastric cancer is 93.4%, and that of stage IB is 87.0%. Comparing these data, adjuvant chemotherapy or/and neoadjuvant chemotherapy will be needed even for early gastric cancer when lymph node metastasis is suspected.

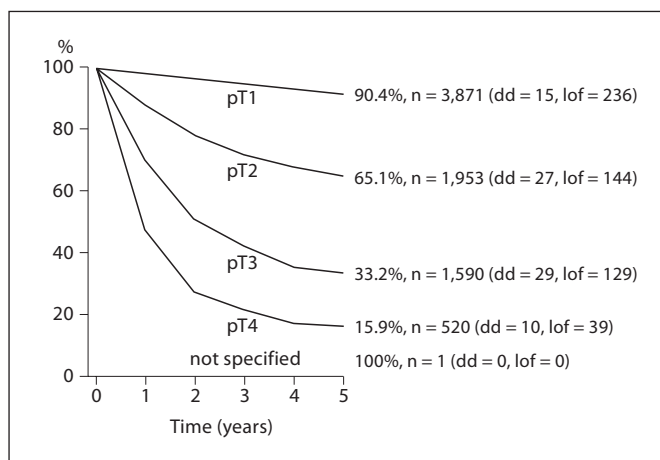


Fig. 2. Overall survival and depth of invasion. pT1 is early cancer. The 5-year survival following early gastric cancer is >90%. dd = Data defect; lof = loss of follow-up.

References

- 1 Japanese Society for Gastric Cancer: The General Rules for the Gastric Cancer Study. Tokyo, Kanehara, 2004.
- 2 Maruyama K, Kaminishi M, Hayashi K; Japanese Gastric Cancer Association Registration Committee: Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. *Gastric Cancer* 2006;9:51–66.
- 3 Japan Gastric Cancer Association (eds): Guidelines for Gastric Cancer Treatment, ed 1. Tokyo, Kanehara, 2001.
- 4 Japan Gastric Cancer Association (eds): Guidelines for Gastric Cancer Treatment, ed 2. Tokyo, Kanehara, 2004.
- 5 Ishikawa M, Kitayama J, Kaizaki S: Prospective randomized trial comparing Billroth I and Roux-en-Y procedures after distal gastrectomy for gastric carcinoma. *World J Surg* 2005;29:1415–1420.
- 6 Adachi S, Inagawa S, Enomoto T: Subjective and functional results after total gastrectomy: prospective study for longterm comparison of reconstruction procedures. *Gastric Cancer* 2003;6:24–29.
- 7 Nomura E, Shinohara H, Mabuchi H: Post-operative evaluation of the jejunal pouch reconstruction following proximal and distal gastrectomy for cancer. *Hepatogastroenterology* 2004;51:1561–1566.
- 8 Maki T, Shiratori T, Hatafuku T, Sugawara K: Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. *Surgery* 1967;61:838–845.
- 9 Hiki N, Kaminishi M: Pylorus-preserving gastrectomy in gastric cancer surgery-open and laparoscopic approaches. *Langenbecks Arch Surg* 2005;390:442–447.
- 10 Shibata C, Shiiba KI, Funayama Y: Outcomes after pylorus-preserving gastrectomy for early gastric cancer: a prospective multicenter trial. *World J Surg* 2004;28:857–861.
- 11 Hiki N, Shimoyama S, Yamaguchi H, Kubota K, Kaminishi M: Laparoscopy-assisted pylorus-preserving gastrectomy with quality controlled lymph node dissection in gastric cancer operation. *J Am Coll Surg* 2006; 203:162–169.
- 12 Adachi Y, Shiraishi N, Kitano S: Modern treatment of early gastric cancer: review of the Japanese experience. *Dig Surg* 2002;19: 333–339.
- 13 Hiki N, Shimizu N, Yamaguchi H, Imamura K, Kami K, Kubota K, Kaminishi M: Manipulation of the small intestine as a cause of the increased inflammatory response after open compared with laparoscopic surgery. *Br J Surg* 2006;93:195–204.
- 14 Aikou T, Kitagawa Y, Kitajima M: Sentinel lymph node mapping with GI cancer. *Cancer Metastasis Rev* 2006;25:269–277.
- 15 Kitagawa Y, Kitajima M: Diagnostic validity of radio-guided sentinel node mapping for gastric cancer: a review of current status and future direction. *Surg Technol Int* 2006;15: 32–36.

Surgical Treatment of Advanced Gastric Cancer: Japanese Perspective

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Key Words

Esophagogastric junction · Gastric cancer, advanced · Surgical treatment

Abstract

The results of clinical trials regarding surgery of curable advanced gastric cancer and esophagogastric junction (EGJ) tumors are reviewed and summarized. Four clinical trials have evaluated D2 dissection for curable gastric cancer in the West. Two large trials in the UK and the Netherlands failed to prove the efficacy of D2 dissection. However, these trials had critical weak points. As they were carried out in a number of hospitals where there was no experience with this surgery, the quality of surgery and postoperative care were very poor making the hospital mortality unacceptably high. After these trials, an Italian group started a phase II study in 8 hospitals with a relatively high volume to confirm the safety of this procedure for Caucasians. They achieved 3% mortality, which was much smaller than that of even D1 in the former trials. These results first highlighted the importance of learning and hospital volume in D2 dissection. Survival results of the Dutch trial showed some difference between D1 and D2, but the difference was not statistically significant. This was attributed to the high hospital mortality and poor quality of surgery, especially low compliance of D2 and the high rate of extension of D1, making this comparison similar to that between D1.3 and D1.7. The results of

the phase III study by the Italian group are awaited. Recently a Taiwanese trial proved the benefit of D2 dissection over D1 in a phase III trial. This was a single institutional trial with a sample size of 221 patients. The 5-year survival rate of D2 and D1 was 59.5 and 53.6%, respectively ($p = 0.04$). The Dutch trials for EGJ tumors showed a large difference in overall survival between the transthoracic and transhiatal approach for Siewert type 1 and 2 tumors, but this was not statistically significant, most likely due to the small sample size. In the subgroup analysis, they demonstrated that there was no survival difference in Siewert type 2 but a large difference in Siewert type 1. A Japanese study showed that there is no benefit to the thoraco-abdominal approach over the transhiatal approach for EGJ tumors whose invasion in the esophagus is 3 cm or less. These two trials clearly demonstrated that mediastinal dissection through a right thoracotomy is recommendable for Siewert type 1, while the transhiatal approach should be considered as standard for Siewert type 2.

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Background

In the guidelines of the Japan Gastric Cancer Association, standard surgery for curable advanced gastric cancer is defined as a more than 2/3 gastrectomy with D2 dissection [1]. With the results of several important

Table 1. Morbidity and mortality after D2 dissection and hospital volume

| Trial | Type | n | Number of patients per hospital per year | Mortality % | Morbidity % | Reference |
|---------------|----------|-----|--|-------------|-------------|----------------------|
| Hong Kong | RCT | 30 | 7.5 | 3 | 57 | Robertson et al. [7] |
| MRC | RCT | 200 | 1.5 | 13 | 46 | Cuschieri et al. [8] |
| Dutch | RCT | 331 | 1.0 | 10 | 43 | Bonenkamp et al. [2] |
| Taiwanese | RCT | 211 | 18.5 | 0 | 17 | Wu et al. [16] |
| IGCSG | Phase II | 191 | 8.0 | 3 | 21 | Degiuli et al. [4] |
| IGCSG | RCT | 82 | 4.3 | 0 | 16 | Degiuli et al. [6] |
| Italian study | Retro | 451 | 21.5 | 2 | 17 | Roviello et al. [9] |

RCT = Randomized controlled trial; MRC = Medical Research Council; IGCSG = Italian Gastric Cancer Study Group.

clinical trials, not only in surgery but also multidisciplinary treatment, this policy of the Japanese guidelines might be challenged. In this article, the Japanese perspective of curative surgery for advanced gastric cancer is explained.

Results of European Trials

There have been four European clinical trials on D2 dissection for curable gastric cancer [2–5]. Three of them were phase III trials and the remainder was the only phase II trial in the world. The phase III trials were carried out by the Medical Research Council (MRC) [3], the Dutch Gastric Cancer Group (DGCG) [2] and the Italian Gastric Cancer Study Group (IGCSG) [5]. The first two trials have already shown negative results, while the long-term results of the last one are awaited. After the first two large phase III trials showed quite high hospital mortality after D2 dissection on Caucasians, the IGCSG started with a phase II study to confirm the safety of the D2 dissection in their population [4].

Morbidity and Mortality of D2 Dissection in These Trials

The Dutch and the MRC studies showed extremely high hospital mortality after D2 dissection, 10 and 13%, respectively. Such a high mortality is no longer accepted for any cancer surgery today. These results were heavily criticized and attributed to a very low hospital volume [6]. Table 1 shows the clear negative correlation between hospital volume and hospital mortality after D2 dissection in the literature. This high mortality was also attributed to splenectomy and pancreatectomy. Especially in the

MRC trial, many surgeons thought that D2 distal gastrectomy included splenectomy, and splenectomy was carried out in many distal gastrectomy cases [10]. This was based on the misunderstanding of the definition of D2 gastrectomy by the Japanese Research Society for Gastric Cancer [11]. In Japan, splenectomy was included in D2 dissection only when a total gastrectomy was carried out. Together with thorough lymph node dissection of the lesser curvature, splenectomy causes serious ischemia of the remnant stomach, necrosis of the remnant stomach or anastomotic leakage. This was also the case in the DGCG trial [12]. In the multivariate analysis of hospital mortality, splenectomy was one of the factors most responsible for mortality. The lack of experience in treating major surgical complications after D2 dissection, namely, anastomotic leakage, pancreatic fistula (juice leak) or intra-abdominal abscess, led to a much higher mortality than a Japanese specialist center where a few hundred patients were treated yearly (table 2) [6]. With less than a few cases yearly, surgeons can never learn how to treat these major complications to avoid treatment-related death. This high mortality after D2 dissection in the Dutch trial might also be attributed to the greater fragility of the Dutch compared with the Japanese. However, the results of another Dutch trial comparing a transthoracic esophago-gastrectomy via right thoracotomy with a transhiatal approach for esophagogastric junction (EGJ) tumors showed a much lower mortality in the both treatment arms, 4% for the former and 2% for the latter [13]. This trial was carried out exclusively in two major cancer hospitals which have a reasonably high hospital volume. This suggests that high mortality in the D1/D2 trial was not attributed to the fragility of the Dutch patients but to the very low hospital volume.

Table 2. Mortality after postoperative major surgical complications

| Complication | Dutch trial (n = 711) | | | NCCH trial (1982–1987; n = 1,197) | | | p |
|-------------------------------|-----------------------|-------------------|------|-----------------------------------|-------------------|------|--------|
| | deceased patients | affected patients | % | deceased patients | affected patients | % | |
| Leakage | 19 | 46 | 41.3 | 12 | 84 | 14.3 | 0.0005 |
| Distal | 9 | 22 | 40.1 | 2 | 23 | 8.7 | 0.012 |
| Total | 10 | 24 | 41.7 | 10 | 60 | 16.7 | 0.0047 |
| Abscess or pancreatic fistula | 19 | 91 | 20.9 | 2 | 75 | 2.7 | 0.0004 |

NCCH = National Cancer Center Hospital.

After these two trials with dismal short-term results, the IGCSG started a phase II trial to confirm the safety. Actually a 3% mortality was found in 8 hospitals with a total of 191 patients [4]. They avoided the routine use of distal pancreatectomy in cases of total gastrectomy; instead they adopted pancreas-preserving total gastrectomy, the so-called Maruyama technique [5]. Thus they avoided splenectomy in distal gastrectomy and distal pancreatectomy in total gastrectomy. The morbidity and mortality shown by the phase II study was confirmed by the results of the interim analysis of the IGCSG phase III trial. Hospital mortality was 1.3% after D1 but 0% after D2 gastrectomy in this study [6].

Survival Results after D2 Dissection

In the MRC trial, the survival curve of D2 was never better than that of D1 until the end of the trial. In the Dutch trial, the survival curve of D2 caught up with that of D1 after 4 years and remained superior, but the difference between D1 and D2 survival never reached statistical significance. Practically, in the MRC trial, there was no quality control of surgery and the quality seemed poor due to the mortality. In the Dutch trial, there were several efforts to control the quality of performance including direct tuition of the D2 dissection in the operation theater and quality evaluation by the number of dissected nodes. According to their results, there were many cases in the D1 group where more extended dissection than D1 was actually carried out and many patients in the D2 group underwent less than D2 dissection [14]. Eventually they compared D1.3 versus D1.7, for example, minimizing the difference between the arms. Low-quality surgery together with a much higher mortality immediately after surgery could explain why D2 dissection was not found to be beneficial. In fact, the Italian group showed much better survival results in their phase II trial than those of

the Dutch trial [15]. The 5-year survival rates for stages IA, IB, II, IIIA and IIIB were 93, 88, 60, 40 and 20%, respectively, while those in the Dutch trial were 81, 61, 42, 28 and 13%, respectively. Survival results of the phase III study by the IGCSG are awaited.

Results of Taiwanese Trial

Recently a Taiwanese hospital published the results of a phase III study comparing D1 versus D2/3 surgery for curable gastric cancer in a single institution [16]. Their D3 includes lymph node stations in the hepatoduodenal ligament, on the superior mesenteric vein, behind the common hepatic artery and on the posterior pancreatic surface in addition to D2 dissection, according to the 1st English Edition of the Japanese Classification of Gastric Carcinoma [17]. They showed statistically significant improvement in survival by D2/3 surgery over D1. The 5-year overall survival of D2/3 and D1 was 59.5 and 53.6%, respectively ($p = 0.04$; fig. 1). This study included only three surgeons at a single institution, therefore the quality of surgery in this study seemed to be more identical than in multicenter trials. This is the first randomized controlled study which showed significantly better overall survival of D2/3 surgery than D1 in the world. There are several remarkable differences between this study and the Dutch study. Due to the much higher hospital volume and good quality control at a single institution, the hospital mortality after D2/3 was 0% in this study, while it was as high as 10% in the Dutch trial. More patients in the Taiwanese study had antral tumors and underwent distal subtotal gastrectomy than the Dutch trial. The proportion of those who underwent distal subtotal gastrectomy in this study and the Dutch study was 76 and 66%, respectively. Due to the rather small sample size and

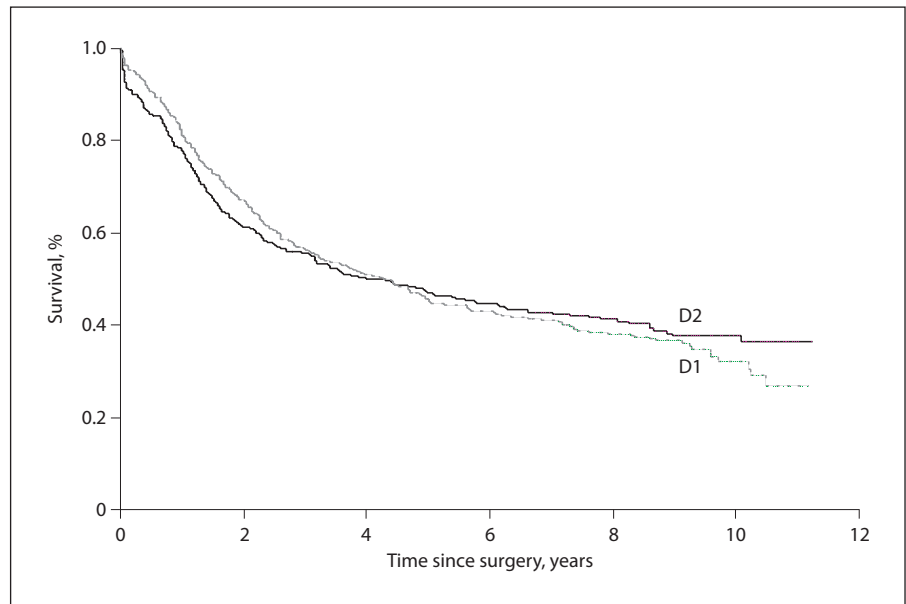


Fig. 1. Overall survival curves of the entire patient population by treatment groups in the Dutch trial.

modest survival benefit, this study cannot be considered as solid evidence for the superiority of D2 over D1 dissection.

Results of Adjuvant Chemoradiotherapy

A phase III study comparing surgery alone with postoperative adjuvant chemoradiotherapy (CRT), the INT0116/SWOG9008, showed a large survival benefit of CRT for curable gastric cancer; the median survival time of surgery alone was 27 months, compared with 36 months for CRT [18]. The hazard ratio for death was 1.35 (95% CI 1.09–1.66; $p = 0.005$). In this trial, the tested arm included curative surgery and radiation therapy of 45 Gy with combination chemotherapy using fluorouracil and leucovorin (5 courses of 5-day continuous infusion, including 2 courses of concomitant administration). However, detailed analysis of the type of surgery revealed that 54 and 36% of the patients underwent D0 and D1 surgery, respectively, while only 10% underwent D2 dissection. Although there was no statistically significant interaction between the subgroups divided by the degree of lymph node dissection and the effect of treatment, a benefit from treatment was observed only in the D0 or D1 group in the subset analysis [19]. In the retrospective detailed analysis, the researchers of this study found that surgical undertreatment clearly undermined the survival of patients [20]. Thus this study for the first time proved

the efficacy of local control by radiation for gastric cancer and proved that limited surgery alone cannot be sufficient treatment for this cancer.

The patient population enrolled in the test arm of this study was by chance quite similar to the population enrolled in a Japanese clinical trial comparing surgery alone with surgery followed by adjuvant CTX (JCOG9206-2) [21]. Table 3 shows the tumor and patient characteristics of the 2 groups. Most of the prognostic factors, i.e., histological type, tumor location, age, tumor size, and, most important, tumor depth, were reasonably comparable between the groups. Although these 2 groups were the patients of two different trials with two different treatment methods, they are identical and therefore the treatment results are more or less comparable. The 5-year overall survival was 42 and 61% in the INT0116 and JCOG9206-2, respectively. This suggests strongly that D2 surgery alone might produce better survival than limited surgery followed by CRT and that the effect of adjuvant CTX might not be expected after D2 as suggested by the subgroup analysis.

Surgical Treatment for Esophagogastric Junction Tumors

Hulscher et al. [13] reported the results of a phase III trial for Siewert type 1 and 2 tumors, comparing two surgical approaches, a transthoracic esophagogastrectomy

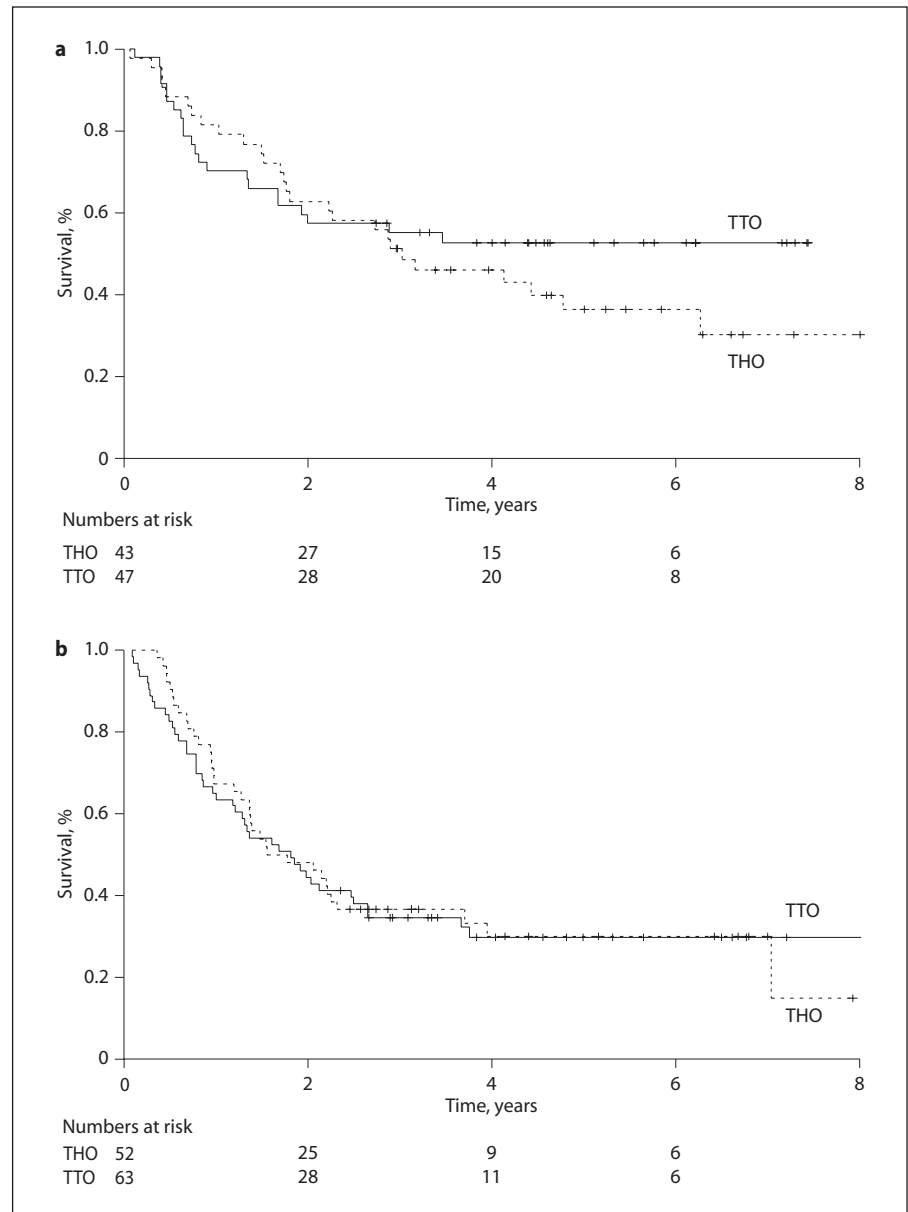


Fig. 2. Overall survival curves in patients with Siewert type 1 (a) and Siewert type 2 (b) tumors, by treatment groups. THO = Transthoracic esophagectomy; TTO = transhiatal esophagectomy.

via right thoracotomy with transhiatal one. The overall survival in the entire study population did not show statistically significant differences between the 2 groups. However, the actual difference in the survival curves was impressive and the overall 5-year survival rate was 29% for the transhiatal approach and 39% for the transthoracic one ($p = 0.38$; fig. 1). In the subgroup analysis according to the Siewert classification, the difference in overall 5-year survival was as large as 17% (95% CI -3 to 37%) for Siewert type 1 ($n = 90$), while it was only 1% for Siewert type 2 ($n = 115$; fig. 2) [22]. Due to the small sam-

ple size, this study was not able to show any statistically significant difference, but the results strongly suggest that thorough mediastinal dissection via right thoracotomy is needed for Siewert type 1 but not for type 2. With higher morbidity after transthoracic dissection, the transhiatal approach might be better treatment for Siewert type 2.

Sasako et al. [23] reported the results of a phase III trial for Siewert type 2 and 3 tumors, comparing a left thoraco-abdominal approach versus a transhiatal one. All these tumors were diagnosed to have esophageal in-

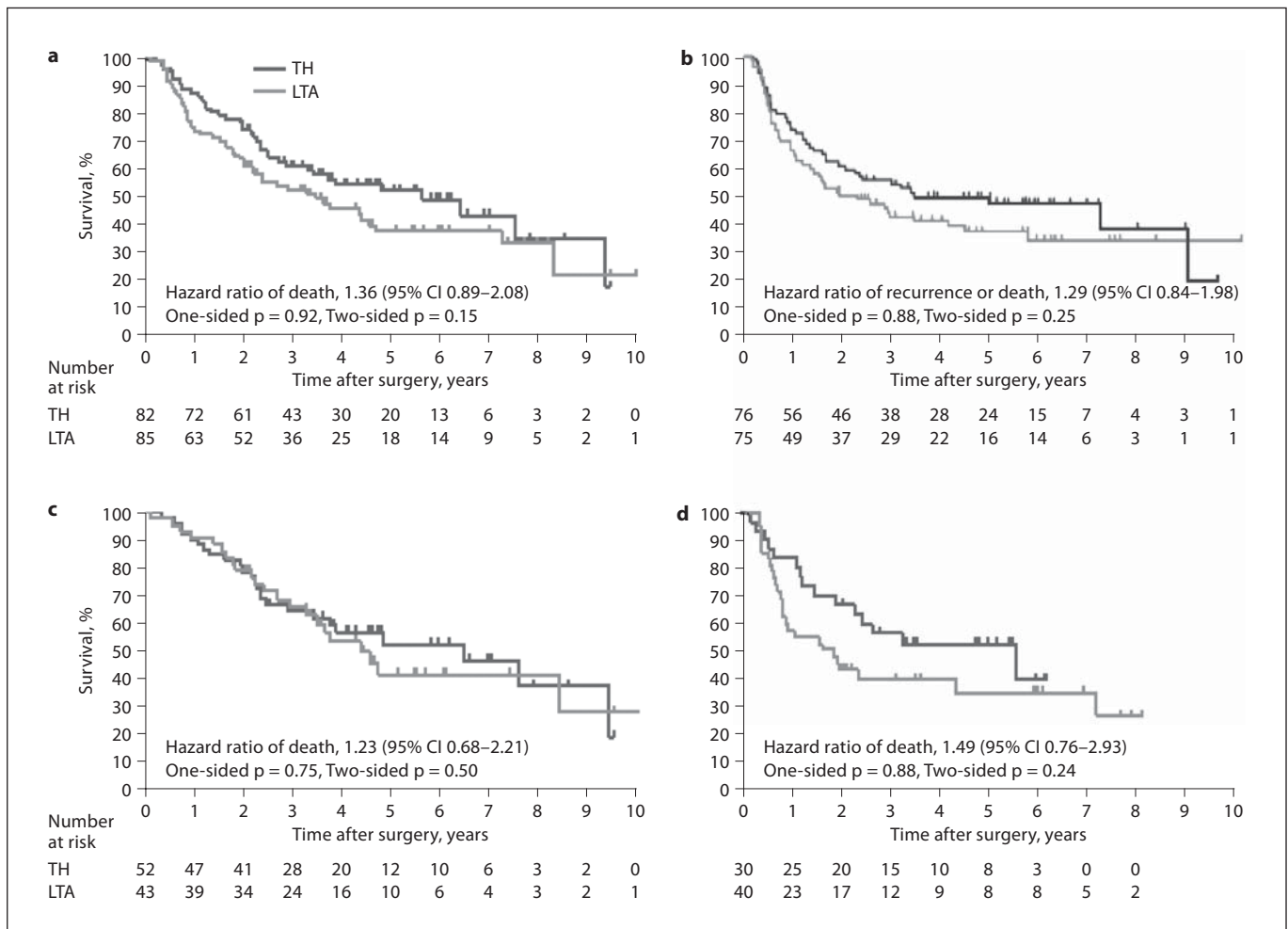


Fig. 3. Overall survival (a) and disease-free survival (b) of the entire patient population and overall survival in patients with Siewert type 2 (c) and type 3 (d) tumors by treatment groups. TH = Transhiatal; LTA = left thoraco-abdominal. Reprinted with permission from *The Lancet Oncology* [23].

Table 3. Comparison between the INT0116 study and JCOG9206-2 study

| | IT0116/SWOG9008 | JCOG9206-2 |
|-------------------------------|--|--------------------------------------|
| Surgery (D0/1/2), % | 54/36/10 | 4/67/33 |
| Adjuvant | Rad (45 Gy)+CX (5FU+LV) | CDDP+5FU+UFT (50%), none (50%) |
| Number of patients | 281 (tested arm) | 268 (control = 133, tested = 135) |
| Tumor location | A (53%), Corp (24%), cardia (21%), multifocal (2%) | L (31%), M (32%), U (28%), wide (9%) |
| pT (T1/T2/T3/T4) | 14/74/175/18 | 5/87/165/11 |
| Proportion of T3/4, % | 69 | 66 |
| Node positive, % | 85 | 72 |
| TRD | 3 (1.1%) | 4 (1.5%) |
| Overall survival (5 years), % | 42 | control 61, tested 62 |

Rad = Radiation; CX = chemotherapy; LV = leucovorin; 5FU = 5-fluorouracil; CDDP = cis-diamminedichloroplatinum; UFT = uracil-ftegafur; A = antrum; Corp = gastric body; L = distal one third; M = middle one third; U = upper one third; wide = wide spread; TRD = treatment-related death.

vasion of 3 cm or less. They clearly demonstrated that there was no survival benefit from the left thoraco-abdominal approach which was accompanied by a much higher morbidity and more remarkable deterioration of pulmonary function than the transhiatal approach. The subgroup analysis showed no survival benefit for both Siewert type 2 and 3. Especially for Siewert type 3, the

transhiatal approach showed much better survival than the left thoracotomy approach (fig. 3).

From these two trials, the transhiatal approach is regarded as the standard treatment for Siewert type 2 and 3 tumors, while the transthoracic approach via right thoracotomy is recommended for Siewert type 1 tumors.

References

- Nakajima T: Gastric cancer treatment guideline in Japan. *Gastric Cancer* 2002;5:1-5.
- Bonenkamp JJ, Hermans J, Sasako M, van De Velde CJ, et al; Dutch Gastric Cancer Group: Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;340:908-914.
- Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P: Patient survival after D1 and D2 resection for gastric cancer: long-term results of the MRC randomized surgical trial. *Br J Cancer* 1999;79:1522-1530.
- DeGiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F: Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. *J Clin Oncol* 1998;16:1490-1493.
- Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okabayashi K: Pancreas-preserving total gastrectomy for proximal gastric cancer. *World J Surg* 1995;19:532-536.
- DeGiuli M, Sasako M, Calgaro M, Garino M, Rebecchi F, Mineccia M, Scaglione D, Andreone D, Ponti A, Calvo F: Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. *Eur J Surg Oncol* 2004;30:303-308.
- Robertson CS, Chung SC, Woods SD, et al: a prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. *Ann Surg* 1994;220:176-182.
- Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P; Surgical Co-operative Group: Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised surgical trial. *Lancet* 1996;347:995-999.
- Roviello F, Marrelli D, Morgagni P, de Manzoni G, Di Leo A, Vindigni C, Saragoni L, Tomezzoli A, Kurihara H, Italian Research Group for Gastric Cancer: Survival benefit of extended D2 lymphadenectomy in gastric cancer with involvement of second level lymph nodes: a longitudinal multicenter study. *Ann Surg Oncol* 2002;9:894-900.
- Sasako M: Principles of surgical treatment for curable gastric cancer. *J Clin Oncol* 2003;21(suppl):274s-275s.
- Japanese Research Society for the Gastric Cancer: The general rules for the gastric cancer study in surgery and pathology. *Jpn J Surg* 1981;11:418-425.
- Sasako M: Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. *Br J Surg* 1997;84:1567-1571.
- Hulscher JBF, van Sandick JW, de Boer AGEM, Wijnhoven BPL, Tijssen JGP, Fockens P, Stalmeier PFM, ten Kate FJW, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002;347:1662-1669.
- Bunt TMG, Bonenkamp JJ, Hermans J, van de Velde CJH, Arends JW, Fleuren G, Bruijn JA: Factors influencing noncompliance and contamination in a randomized trial of 'Western' (R1) versus 'Japanese' (R2) type surgery in gastric cancer. *Cancer* 1994;73:1544-1551.
- DeGiuli M, Sasako M, Ponti A, Calvo F: Survival results of a multicenter phase II study to evaluate D2 gastrectomy for gastric cancer. *Br J Cancer* 2004;90:1727-1732.
- Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AFY, Lui WY, Peng JW: Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;7:309-315.
- Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma, ed 1. Tokyo, Kanahara, 1995, p 15.
- Macdonald JS, Smalley SR, Benedetti J, Este SANC, Stemmermann NG, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-730.
- Macdonald JS: Postoperative combined radiation and chemotherapy improves disease-free survival (DFS) and overall survival (OS) in resected adenocarcinoma of the stomach and gastroesophageal junction: update of the results of Intergroup Study INT-0116 (SWOG 9008). Virtual Meeting of ASCO GI Symposium.
- Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T: Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002;9:278-286.
- Miyashiro I, Furukawa H, Sasako M, Yamamoto S, Nashimoto A, Nakajima T, Kinoshita T, Kobayashi O, Arai K; Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group: No survival benefit with adjuvant chemotherapy for serosa-positive gastric cancer (JCOG9206-2). *Proc 2005 Gastrointestinal Cancer Symp*, p 84.
- Hulscher JBF, van Lanschot JJ: Individualised surgical treatment of patients with an adenocarcinoma of the distal oesophagus or gastro-oesophageal junction. *Dig Surg* 2005;22:130-134.
- Sasako M, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, Nashimoto A, Hiratsuka M: Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol* 2006;7:644-651.

Surgical Treatment for Digestive Cancer

Current Issues – Colon Cancer

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Key Words

Colon cancer · Colonic resection · Lymphadenectomy, D3

Abstract

Background: Due to the westernization of the diet in Japan, the incidence of colorectal cancer has increased 4.5 times in the last 25 years. In this review, the recent results of surgical treatment for colonic cancer and the future perspectives in Japan are described. **Materials and Methods:** A multi-institutional registry of large bowel cancer in Japan of 10,809 patients with colonic cancer treated from 1991 to 1994 was investigated. The data have been published in the Guidelines of the Japanese Society for Cancer of the Colon and Rectum (2005). Regarding laparoscopic surgery, 1,495 patients with colon cancer were examined in a multicenter study between April 1993 and August 2002. **Results:** Radical resection with a curative intent is appropriate for 83–99% of the patients with stage I–III localized colon carcinoma. Adequate lymphadenectomy, including paracolic, intermediate and principal node dissection (D3 lymphadenectomy), is of critical importance for both the accurate staging and local control of the disease. This treatment protocol has now been accepted as a ‘standard’ operation by Japanese colorectal surgeons. For patients undergoing a curative resection for colon cancer, the 5-year survival rates vary between 62 (stage III) and 91% (stage I). Adjuvant chemotherapy using 5-FU/leucovorin or oral compounds is commonly administered to patients with stage III disease. Laparoscopic surgery for colonic can-

cer yielded a comparable oncological outcome to that reported for conventional open surgery in the Japanese registry for all disease stages. **Conclusion:** Radical resection with a D3 lymphadenectomy provided satisfactory 5-year survival for patients with stage I–III colon cancer in Japan. However, the survival of patients with stage IV disease is still unsatisfactory (only a 14% 5-year survival). Any further improvements depend on both identifying such patients at an earlier stage as well as developing new and effective treatment modalities.

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Introduction

Colorectal cancer is a significant health problem in Japan. In 1998 the annual age-adjusted colon cancer incidence per 100,000 individuals in Japan was 42.3 for males and 24.4 for females, and these rates have increased 3.2 times over those reported in 1975 (10.9 for males, 9.7 for females), and they are continuing to increase [1]. In 2001 colorectal cancer was the fourth leading cause of cancer death in men and the second leading cause in women, and it is anticipated to become the leading cause of cancer death in Japan by 2015 due to environmental factors and the changing dietary habits of Japanese people, which are increasingly becoming similar to those of Western countries [2].

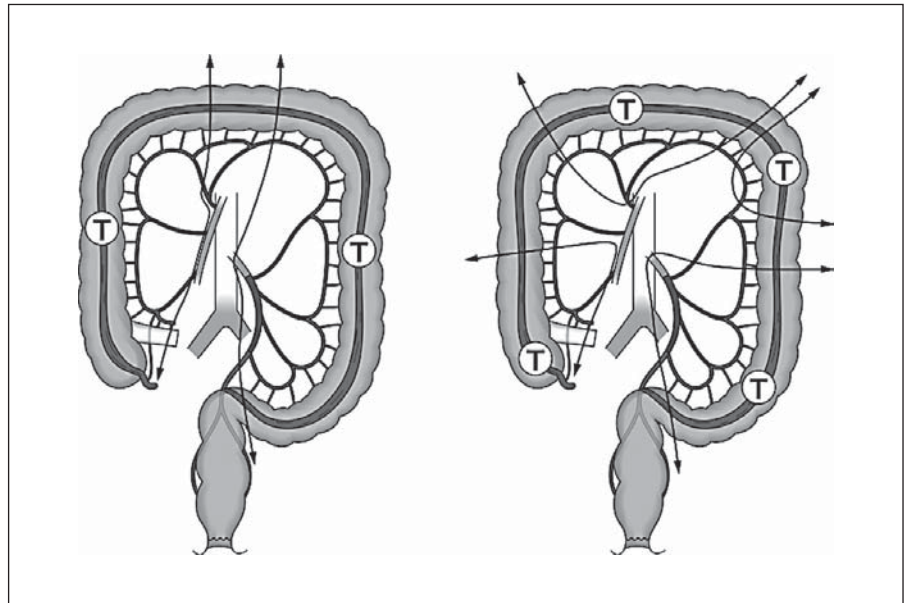


Fig. 1. Extent of resection for carcinoma of the colon. T = Tumor.

Principles of Resection

The principle objective of resection for colon carcinoma is to remove the primary tumor along with its lymphovascular supply. Since the lymphatics of the colon accompany the main arterial supply, the length of the resected bowel depends on which vessels supply the segment involved in the cancer [3]. Before 2005, the Japanese General Rules for Clinical and Pathologic Studies on Cancer of the Colon and Rectum (JGR) recommended that a colectomy should be performed with at least 5- to 10-cm-long proximal and distal margins, and that the regional arterial blood supply should be taken at its origin, thus assuring an adequate mesenteric resection. In the new version of these rules (2006), the cut edge of the bowel is strictly standardized with careful attention being paid to the main arterial supply of the tumor [4].

Lesions of the cecum, ascending colon, and hepatic flexure are usually treated by a right hemicolectomy, because the blood supply to this area comes from the ileocolic and right colic arteries. Figure 1 also shows the extent of a resection for carcinomas of the designated lesions. A left partial colectomy is the preferred operation for tumors involving the distal transverse colon, splenic flexure, and descending colon. In addition, a sigmoidectomy is the standard operation for sigmoid colon cancer.

Stage-Specific Therapy

Stage 0 (Tis N0 M0) and Stage I (T1-2 N0 M0)

Polyyps measuring less than 2 cm in diameter are removed endoscopically because they basically carry no risk of lymph node metastasis. After a polypectomy, the pathologic margins are examined to ensure that they are free of dysplasia. In the case of a positive margin, depth of submucosal invasion of $\geq 1,000 \mu\text{m}$, lymphovascular invasion, or a poorly differentiated histology, an additional surgical resection is recommended because of the risk of local recurrence and metastatic spread. Polyyps measuring >2 cm in diameter or sessile polyyps which could possibly be invasive carcinoma should be removed by surgical resection. In such cases, laparoscopic segmental colectomy is considered to be a good option. The treatment strategy for malignant polyyps is summarized in figure 2.

Stage I and Stage II: Localized Colon Carcinoma (T Any, N0 M0)

The majority of patients with stage I and II colon cancer can be successfully treated by surgical resection. It is recommended that patients demonstrating a depth of invasion of T3 or more undergo adequate colonic resection with a D3 lymph node dissection according to the Japanese guidelines [5]. D3 means complete dissection of the regional lymph nodes including the paracolic, intermediate and the principal lymph nodes (fig. 3).

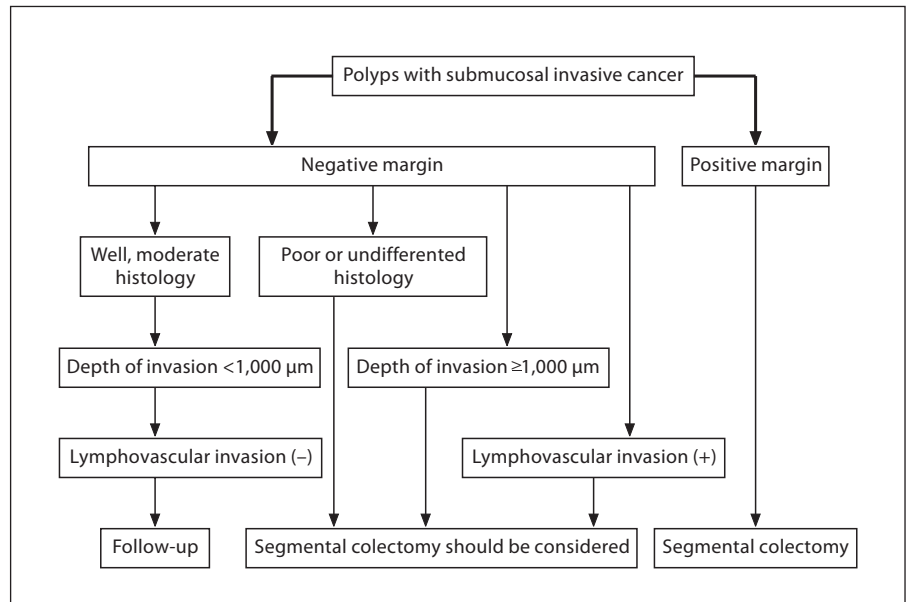


Fig. 2. Treatment strategy for endoscopically resected malignant polyps, according to the Japanese Guidelines for Colorectal Cancer [5] with slight modifications.

Stage III: Lymph Node Metastasis (T Any, N1–3 M0)

Patients with lymph node involvement are at significant risk for both local and distant recurrence, and therefore an adequate colonic resection with a D3 lymph node dissection should be performed. A D3 lymph node dissection contributes not only to the local control of disease but also to accurate staging. Adjuvant chemotherapy is therefore routinely recommended for these patients.

Adjuvant Chemotherapy

Adjuvant chemotherapy is regarded as a standard treatment for patients with stage III colon cancer; however, the use of chemotherapy after surgery in patients with stage II disease remains controversial. Although 5-fluorouracil (5-FU) has been the mainstay of therapy for the last four decades, we have entered into a new era with the development of novel chemotherapy and biological agents. The combination of adjuvant 5-FU, leucovorin (LV), and oxaliplatin has been shown to significantly improve the disease-free survival and it is now considered to be the standard of care for completely resected colon cancer in healthy patients [6–8]. The Japanese Guidelines recommend the use of 5-FU with LV as the standard adjuvant chemotherapy [5]. The availability of oral chemotherapy agents has helped to make administration easier while also helping to avoid the need to use indwelling catheters.

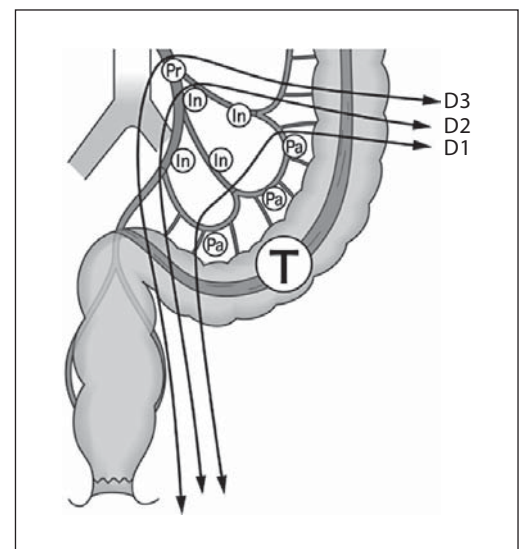


Fig. 3. The extent of dissection of the regional lymph nodes. Pa = Paracolic lymph node; In = intermediate lymph node; Pr = principal lymph node; T = tumor.

Stage IV: Distant Metastasis (T Any, N Any M1)

The pattern of distant metastases in stage IV disease is summarized in table 1. The liver is the most common site of metastasis from colorectal cancer. A surgical resection is the only treatment known to provide a long-term survival and the possibility of a cure in patients with liver metastases.

Table 1. Synchronous distant metastases in colorectal cancer

| | Liver | Lung | Peritoneum | Others | | | | |
|----------------------------|---------------|------------|--------------|-----------|-----------|-----------|------------|------------|
| | | | | bone | brain | Virchow | other | total |
| Colon cancer (15,528) | 11.4% (1,777) | 1.6% (242) | 6.4% (993) | 0.3% (44) | 0.1% (9) | 0.1% (19) | 0.4% (64) | 0.9% (136) |
| Rectal cancer (10,563) | 9.5% (1,002) | 1.7% (180) | 3.0% (314) | 0.3% (36) | 0.1% (8) | 0.01% (1) | 0.5% (57) | 1.0% (102) |
| Colorectal cancer (26,091) | 10.7% (2,779) | 1.6% (422) | 5.0% (1,307) | 0.3% (80) | 0.1% (17) | 0.1% (20) | 0.5% (121) | 0.9% (238) |

From the JSCCR, a multi-institutional registry of large bowel cancer in Japan, 1995–1998.

Table 2. Grading of colorectal liver metastasis (JSCCR, 2006)

| | H1 | H2 | H3 |
|----|----|----|----|
| N0 | A | B | |
| N1 | | | |
| N2 | B | | |
| N3 | C | | |
| M1 | C | | |

H1 = Four or fewer metastatic tumors and the largest hepatic tumor ≤ 5 cm.

H2 = Except H1, H3.

H3 = Five or more metastatic tumors and the largest hepatic tumor > 5 cm.

Regional node status of the primary tumor:

N0 = Node-negative.

N1 = Node-positive, 1–3.

N2 = Node-positive, 4 or more.

N3 = Node-positive along a major named vascular trunk.

Table 3. Five-year survival depending on the grade of liver metastases

| Grade | All cases (473) | Resected cases (378) | Unresected cases (95) |
|-------|-----------------|----------------------|-----------------------|
| A | 50.3% (191) | 52.9% (177) | 14.3% (14) |
| B | 24.5% (161) | 29.6% (121) | 7.7% (40) |
| C | 6.7% (121) | 10.4% (80) | 0% (41) |

The remainder of patients with stage IV disease, except for patients with multiple organ metastases, such as to the liver and lung, require a resection for cure. However, almost all patients with stage IV disease cannot be surgically cured and therefore the focus of treatment should be palliation. Many of these patients require colonic cancer resection because of symptoms of hemorrhaging and/or obstruction.

Liver Metastasis

Liver metastasis is the most common metastatic pattern in colorectal cancer. Synchronous liver metastases are present in 10% of all patients with colorectal cancer and they occur in more than half of all patients with recurrent disease [5]. Of these, 30% are potentially resectable for cure. The indications for a hepatic resection include control of the primary site, no signs of disseminated disease, no signs of hepatic node metastases, a technically feasible operation, and an adequate hepatic function reserve of the patient.

Hepatic resection has been associated with a 27–40% 5-year survival and confers a survival advantage compared to patients not undergoing resection [9–11]. Kato et al. [12] observed a 5-year survival rate of 39% for 585 patients who were resected in a multi-institutional study in Japan. The differences among institutes may be related more to the clinical stages at the time of hepatic resection than the surgeon's skills at the individual institutes. A working group of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) has proposed a new staging system based on the number of lymph node metastases from the primary cancer, the number of liver metastases, and the size of the metastatic nodules (table 2). The new staging system appears to be useful for predicting the prognosis of patients with liver metastases from colorectal cancer (table 3).

Lung Metastasis

Surgical resection is recommended as the first choice for treatment of pulmonary metastases, and the results of the 5-year survival have been reported to range from 30 to 60% in recently reported series [13–15]. Candidate selection is based on the number and location of metastases, the absence of diseases other than pulmonary disease, an adequate pulmonary function reserve, and a good overall medical condition [5].

Table 4. Five-year survival rates based on the JGR classification (1991–1994)

| | Stage 0 | Stage I | Stage II | Stage IIIa | Stage IIIb | Stage IV | All Stage |
|-------------|-------------|-------------|-------------|-------------|------------|-------------|--------------|
| C | 90% (110) | 87% (149) | 81% (252) | 69% (209) | 60% (137) | 10% (225) | 64% (1,082) |
| A | 96% (209) | 91% (257) | 84% (698) | 74% (398) | 57% (254) | 14% (409) | 68% (2,225) |
| T | 95% (176) | 89% (199) | 83% (447) | 70% (270) | 60% (143) | 10% (261) | 68% (1,496) |
| D | 95% (129) | 90% (151) | 83% (267) | 71% (152) | 58% (67) | 19% (115) | 73% (881) |
| S | 95% (559) | 91% (1,149) | 85% (1,373) | 81% (879) | 67% (394) | 17% (781) | 75% (5,135) |
| Colon (C–S) | 95% (1,183) | 91% (1,905) | 84% (3,037) | 76% (1,908) | 62% (995) | 14% (1,791) | 71% (10,819) |

Stage IIIa included T3N1M0, T4N0M0 in this JGR classification (6th version, 1998), but T4N0M0 is classified as stage II in the new version (7th version, 2006) according to the UICC TNM classification.

C = Cecum; A = ascending colon; T = transverse colon; D = descending colon; S = sigmoid colon.

Results of Surgery for Carcinoma of the Colon (from 1991 to 1994)

JSCCR collected data from a national registry in Japan and calculated the 5-year survival rate depending on the primary lesion (table 4). The survival rates generally correlate with the extent of lymph node involvement. Internationally, the TNM classification system is widely used for staging. In the TNM classification, node metastases are classified into three grades, from pN0 to pN2, based on the number of metastatic nodes. In Japan, the JGR have been used as mentioned earlier. In the JGR before 2005, node metastases were classified into four levels, n(-), n1(+), n2(+), and n3(+), based on the distribution of the metastatic nodes. This system accurately classifies both the patient distribution and survival rates; however, it is considered to be too complicated. In the new version of JGR (2006), the extent of nodal metastases is classified into four grades: N0, N1, N2 and N3. Grades N0–N2 correlate with the N categories of the TNM classification, and N3 is defined as invasion of the principal node [4]. The JGR also indicates the region that should be dissected, thus making this method well suited for clinical use.

Laparoscopic Resection of Colonic Cancer

In Japan, laparoscopic surgery for colorectal cancer was first introduced in 1992, and many centers are now performing either laparoscopic or laparoscopically assisted colon resections. To date, many studies have confirmed these methods as resulting in a faster recovery, less pain, shorter hospital stay, and satisfactory short-term oncologic results. However, the long-term oncolog-

ic results of laparoscopic surgery for colorectal cancer still remain unclear.

The Japanese Laparoscopic Surgery Study Group collected the data obtained from 12 main institutes of Japan during the period April 1993 to August 2001. During this period, 1,495 patients underwent a laparoscopic colonic resection. Of the 1,495 patients with colonic cancer, 188 (12.6%) had postoperative complications including: wound infection in 97 cases (60%); bowel obstruction in 31 cases (19%); anastomotic leakage in 22 (14%), and others. Cancer recurred in 61 (4.3%) of the 1,411 curatively treated patients; however, no port site recurrence was found. The 5-year survival rate was 96.6% for the patients with stage I, 94.8% for those with stage II, and 79.6% for those with stage III disease [16].

We cannot compare the current data to those of open surgery series because the findings represent an uncontrolled study. These favorable results of laparoscopic surgery for colon cancer have resulted in this treatment being accepted as a radical operation for potentially curable patients in Japan. However, a randomized prospective trial is necessary in the near future.

Follow-Up and Surveillance

The optimal way to follow patients who have undergone resection for carcinoma of the colon is a subject worthy of some discussion. The main goal of the follow-up is to improve patient survival by making an early diagnosis of recurrence during the asymptomatic stage when radical surgical treatment is still viable. Other goals of follow-up are to enable early treatment of other bowel lesions including polyps and metachronous cancers, to solve surgery-related problems in a timely manner, to provide pa-

Table 5. Comparison between the follow-up guidelines

| | JSCCR ¹ | ASCO | ESMO |
|-------------------------|---|--|---|
| Physical examination | Every 3 months for 3 years then every 6 months up to 5 years | Every 3–6 months for 3 years then every 6 months up to 5 years | Every 3–6 months for 3 years then every 6–12 months up to 5 years |
| CEA | Every 3 months for 3 years then every 6 months up to 5 years | Every 3 months for at least 3 years (stage II or III) | No |
| Chest X-ray Chest CT | Every 6 months for 5 years (X-ray) or annually for 5 years (CT) | No Annually for 3 years (high risk of recurrence) | Annually for 5 years With suspicion |
| Liver sonography | 6 months after surgery then annually up to 5 years | No | Every 6 months for 3 years then annually for 2 years |
| Abdominal CT | Annually for 5 years | Annually for 3 years (high risk of recurrence) | With suspicion |
| Colonoscopy | Annually for 3 years | 3 years after surgery then every 5 years | 1 years after surgery then every 3 years |

¹ Basically for patients with stage III, flexible in patients with lower stage disease.

tients with psychological support, and to evaluate the impact of new therapeutic approaches. However, postoperative follow-up may sometimes be based on a not completely scientific background, including ‘health politics’, ‘national standards’ or ‘class requirements’, namely providing the maximum care possible for patients to avoid being accused of guilt associated with an incurable non-diagnosed recurrence. As a result, Japanese doctors tend to perform intensive follow-up based on national standards. The guidelines of, for example, the JSCCR, the American Society Clinical Oncology and the European Society Medical Oncology confirm these considerations even if these societies all agree on some of the elements while disagreeing on many others regarding performance of an appropriate follow-up (table 5) [17].

Conclusions

In surgical treatment for colon cancer, a colonic resection with a D3 lymph node dissection is widely accepted as the treatment of choice in Japan. A D3 lymphadenectomy contributes to both local control of disease as well as accurate staging without increasing surgical stress, including operation time and blood loss, in comparison to a D2 lymphadenectomy. This may be related to the fact that Japanese patients tend to have a lower body mass index than Western patients. To date, we have obtained a

favorable outcome for the patients with potentially curable colon cancer by means of surgical treatment. However, the prognosis for patients with stage IV disease still remains poor. Multimodal treatment for liver/lung metastases is now being developed and recent systemic chemotherapy trials have demonstrated promising results [7, 18]. Any further improvements in survival rates will depend on both identifying patients earlier in order to surgically treat them in a more timely manner as well as in developing new and effective treatment modalities in the future [19–21].

References

- 1 Japanese Society for Cancer of the Colon and Rectum: Multi-Institutional Registry of Large Bowel Cancer in Japan. Vol 24: Cases Treated in 1998. Tochigi, Registry Committee, 2003.
- 2 Wakai K, Hirose K, Ito K, et al: Dietary risk factors for colon and rectal cancers: a comparative case-control study. *J Epidemiol* 2006;16:125–135.
- 3 Corman ML: *Colon and Rectal Surgery*, ed 5. Philadelphia, Lippincott Williams & Wilkins, 2005, pp 804–856.
- 4 Japanese Society for Cancer of the Colon and Rectum: *General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus*, ed 7 (in Japanese). Tokyo, Kanehara Shuppan, 2006.

- 5 Japanese Society for Cancer of the Colon and Rectum: The Guidelines for Therapy of Colorectal Cancer (in Japanese). Tokyo, Kanehara Shuppan, 2005.
- 6 O'Connell MJ, Laurie JA, Kahn M, et al: Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer. *J Clin Oncol* 1998;16:295–300.
- 7 Goyle S, Maraveyas A: Chemotherapy for colorectal cancer. *Dig Surg* 2005;22:401–414.
- 8 Monga DK, O'Connell MJ: Surgical adjuvant therapy for colorectal cancer: current approaches and future directions. *Ann Surg Oncol* 2006;13:1021–1034.
- 9 Sasson AR, Sigurdson ER: Surgical treatment of liver metastases. *Semin Oncol* 2002;29:107–118.
- 10 Martin LW, Warren RS: Current management of colorectal liver metastases. *Surg Oncol Clin North Am* 2000;9:853–876.
- 11 Penna C, Nordlinger B: Surgery and local treatments of liver metastases from colorectal cancer: how to improve results. *Scand J Surg* 2003;92:90–96.
- 12 Kato T, Yasui K, Hirai T, et al: Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy. *Dis Colon Rectum* 2003;46(suppl):S22–S31.
- 13 McCormack PM, Burt ME, Bains MS, et al: Lung resection of colorectal metastases. 10-year results. *Arch Surg* 1992;127:1403–1406.
- 14 Ike H, Shimada H, Ohki S, et al: Results of aggressive resection of lung metastases from colorectal carcinoma detected by intensive follow-up. *Dis Colon Rectum* 2002;45:468–475.
- 15 Saito Y, Omiya H, Kohno K, et al: Pulmonary metastasectomy for 165 patients with colorectal carcinoma: a prognostic assessment. *J Thorac Cardiovasc Surg* 2002;124:1007–1013.
- 16 Kitano S, Kitajima M, Konishi F, et al: A multicenter study on laparoscopic surgery for colorectal cancer in Japan. *Surg Endosc* 2006;20:1348–1352.
- 17 Destri GL, Cataldo AD, Puleo S: Colorectal cancer follow-up: useful or useless? *Surg Oncol* 2006;15:1–12.
- 18 Saunders M, Iveson T: Management of advanced colorectal cancer: state of art. *Br J Cancer* 2006;95:131–138.
- 19 Khan S, Tan YM, John A, et al: An audit of fusion CT-PET in the management of colorectal liver metastases. *Eur J Surg Oncol* 2006;32:564–567.
- 20 Esteves FP, Schuster DM, Halker RK: Gastrointestinal tract malignancies and positron emission tomography: an overview. *Semin Nucl Med* 2006;36:169–181.
- 21 Gasparini G, Longo R, Torino F, et al: Tailored therapy of colorectal cancer: results, challenges and future directions. *Cancer J* 2005;11:175–188.

Current Surgical Management of Rectal Cancer

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Key Words

Lymph node dissection, lateral • Mesorectal excision, total • Rectal cancer

Abstract

The management of rectal cancer has undergone significant evolution over the past decade with improvements in both surgical technique and adjuvant therapies. The progression of surgical management has been of particular interest, as surgery is the only potentially curative treatment. The major goals of surgery are to optimize oncologic outcome and maintain anorectal and genitourinary function. There are presently two approaches to rectal cancer surgery: total mesorectal excision (TME), which is the gold standard in the Western world, and lateral lymph node dissection, which was originally developed in Japan. Although the results of lateral lymph node dissection are similar to TME with prior radiotherapy, low positive lateral lymph node yields, questionable prognostic significance, and high morbidity are the main drawbacks of this procedure. Despite the current quality of these surgical procedures, locoregional treatment is limited as advanced primary rectal cancer may be associated with systemic spread of disease. Adjuvant therapy therefore plays a key role in obtaining further improvement in survival. In this article, evidence for the use and benefits of lateral lymph node dissection surgery for rectal cancer patients in Japan is reviewed, and its application in association with TME and other modalities considered.

Introduction

Treatment of rectal cancer has improved over the past decade with regard to both surgical techniques and adjuvant therapies. These advances have markedly reduced the incidence of recurrent disease while offering sphincter preservation to more patients with lower rectal cancer. Historically, using traditional operative techniques without adjuvant therapy, the outcome was poor and carried with it significant morbidity [1, 2]. Therefore, (neo)adjuvant radiotherapy with or without chemotherapy has been used widely in an attempt to improve long-term outcome for rectal cancer in the Western world. However, surgery is the only potentially curative treatment modality for rectal cancer. In addition, as the main goals of surgery for rectal cancer are to optimize oncologic outcome and maintain anorectal and genitourinary function, the progression of surgical management has been of major interest. The most important advance in operative technique was the advent of total mesorectal excision (TME) proposed by Heald et al. [3] in 1982 as the standard surgical method to achieve good control and to preserve autonomic nerve function [4]. This has been the most important breakthrough in the management of rectal cancer to date.

To improve local control and survival lateral lymph node dissection has been used as a standard procedure for lower rectal cancer in Japan since the late 1970s, whereas in the Western world it has not been frequently

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used. Although the results of lateral lymph node dissection are similar to TME with prior radiotherapy, low positive lateral lymph node yields, questionable prognostic significance, and high morbidity (urinary and sexual dysfunction) are the main reasons against the use of this procedure. Recently, the use of preoperative radiotherapy for rectal cancer has also gradually increased in Japan. Therefore, decisions regarding the optimal surgical treatment for patients with rectal cancer have become more complex, especially with regard to surgical techniques such as lateral lymph node dissection with nerve-sparing and TME.

This article reviews the surgical management of rectal cancer in Japan and discusses major surgical considerations including lateral lymph node dissection and TME. The use of adjuvant therapy such as radiation therapy and chemotherapy in Japan are also reviewed.

Surgical Technique

Rationale of Surgical Treatment and Its Relationship to the Anatomy of Rectal Cancer Spread

In the early 20th century, Miles [5] revealed for the first time that lymphatic spread from rectal cancer occurred in 3 directions – upward, laterally, and downward. He emphasized the importance of including the surrounding regional lymph nodes with complete excision of the rectum and anus, and thus abdominoperineal resection was born. Since then, an understanding of the importance of adequate lymph node dissection for both local recurrence and prognosis has become fundamental to the surgical approach to rectal cancer. With experience, it was recognized that although Miles' concept of the upward zone of lymphatic spread was correct, he had overestimated the incidence of distal and lateral lymphatic spread. In addition, improvement in stapling technology over the past 20 years has led to a dramatic increase in the number of curative sphincter-saving operations. The historical shift from radical abdominoperineal resection for rectal cancer to the use of sphincter-saving techniques has resulted primarily from a better understanding of what constitutes an adequate distal resection margin. In the 1980s, Williams et al. [6] and Pollett and Nicholls [7] proposed that perhaps even a 2-cm distal resection margin was justifiable. However, recent studies indicate that the main reason for local recurrence is lateral spread rather than a positive resection margin [3, 8, 9]. Therefore, the recent emphasis of rectal cancer surgery has been on preservation of function, with dis-

section in appropriate anatomical planes. In 1982, Heald et al. [3] emphasized the importance of recognizing the 'holy plane', in which the surgeon's dissection will encompass the malignancy and yet preserve autonomic neural function. TME was defined as complete excision of the visceral mesorectal tissue to the level of the levators [10]. The use of TME has undoubtedly improved the treatment of patients with rectal cancer in Europe and the United States.

Meanwhile, a different technique for the treatment of rectal cancer was developed in Japan. For rectal cancers, lymphatic spread occurs not only upward to the mesenteric nodes along the superior rectal and inferior mesenteric vessels, but also laterally to the hypogastric, obturator and presacral lymph nodes along the middle rectal, sacral and iliac vessels. Japanese surgeons have reported that the presence of lateral lymph node metastases along the iliac vessels is an important factor for local recurrence in patients with advanced low rectal cancer. Because lateral lymph nodes are not removed by dissection along the 'holy plane', patients with lateral node metastases have an increased risk of local recurrence when treated with TME alone.

Lateral Lymph Node Dissection

Incidence of Metastases, and Prognostic Significance

The reported incidence of lateral lymph node metastases ranges between 8.6 and 17.3% of patients with rectal cancer [11–18]. The local recurrence rate is high and survival rate is poor in patients who have positive lateral lymph nodes, even when compared with patients who have positive mesorectal lymph nodes [19]. In a retrospective analysis of 764 rectal cancer patients, Takahashi et al. [15] examined lateral lymphatic drainage anatomically and demonstrated that 66 patients had lateral lymph node metastases, which constituted 8.6% of all the cases and 16.4% of low-lying cases. As all of those patients underwent lateral lymph node dissection, resulting in a 5-year survival rate of 75%, the authors concluded that lateral lymphatic flow from low-lying rectal cancer passes outside the boundaries of TME but within the range of curative surgery by extended lateral lymph node dissection [15]. Several retrospective studies have shown a prognostic significance of lateral lymphatic spread in rectal cancer and an improved survival rate after resection with extended lateral lymph node dissection compared to conventional resection without lateral lymph node dissection [14, 15, 17, 20] (table 1).

Table 1. Oncologic outcome for potentially curative radical rectal resection of rectal cancer according to the principles of lateral lymph node dissection

| Reference | Year | Patients | Stage | Local recurrence | 5-Year survival |
|-----------------------|------|----------|------------------------------|---|--|
| Moriya et al. [14] | 1997 | 448 | I, 88 II, 142 III, 218 | I, 3.4% II, 2.8% III, 16.1% (all 9.4%) | Dukes C, 55% Lateral node involvement, 43% |
| Mori et al. [20] | 1998 | 157 | II, 157 | 7.40% | Lateral node involvement 32.1% (1975–1989) 43.3% (1988–1996) |
| Takahashi et al. [15] | 2000 | 764 | I, II, 425 III, 339 | I, II, 1.9% III, 15.3% (all 7.8%) | Lateral node involvement, 42.4% |
| Morita et al. [17] | 2003 | 212 | – | all 6.3% | Lateral node involvement, 47% |

Autonomic Nerve Preservation

Extended dissection has occasionally impaired urinary and male sexual function, resulting in poor post-operative quality of life (QOL), as the pelvic autonomic nervous system was often sacrificed during lateral lymph node dissection [21–23]. To address this problem, several reports from Japanese surgeons have demonstrated various pelvic autonomic nerve preservation (ANP) procedures with lateral lymph node dissection which resulted in improved urinary and sexual function compared to previous results [20, 24, 25]. Mori et al. [20] combined ANP resection with lateral lymph node dissection in patients with advanced lower rectal cancer. In cases of ANP with lateral dissection the local recurrence rate was 4.8% overall and 7.4% in the Dukes C group. Although sexual function remained problematic, post-operative urinary function was good or fair in all ANP patients. In a retrospective analysis of 214 rectal cancer patients who underwent pelvic ANP, Sugihara et al. [24] evaluated oncologic outcome and urinary and male sexual function to classify four types of nerve-preservation procedures, for example unilateral pelvic plexus resection. They concluded that appropriate pelvic ANP should be applied with consideration of the balance between curability and QOL. It is therefore thought to be excessive to routinely perform extended lateral lymph node dissection with sacrifice of the autonomic nerves as a standard operation for rectal cancer, making precise preoperative assessment of the extent of local cancer spread important when determining the appropriate treatment strategy.

Prognostic Valuables in Patients with Lateral Lymph Node Metastases

Ueno et al. [26] examined the prognostic variables in rectal cancer patients with lateral lymph node metastases and showed that the most important factors determining prognosis are: distant metastasis; the total number of lymph nodes involved; circumferential resection margin, and age. They also confirmed that the histology in the submucosal invasive frontal region (tumor budding, poor differentiation, vascular invasion) reflects the extent of local spread [27]. Some reports have suggested limiting systemic lateral node dissection to patients with lateral lymph node metastases. Even after extended lateral lymph node dissection, the prognosis of patients with autonomic nerve plexus involvement was unfavorable [28]. Matsumoto et al. [29] also studied the feasibility of ANP surgery for advanced rectal cancer based on an analysis of micrometastases. In the study, patients with micrometastases to tissues surrounding the pelvic plexus had a poor outcome, even after extended dissection [29]. These results should encourage the use of adjuvant therapy for high-risk patients even after extended lymph node dissection.

Other Modalities

Radiation Therapy for Local Control

Radiation therapy of resectable rectal cancer has been widely accepted in the Western world. The use of radiation therapy reduces the risk of local recurrence and also

controls subclinical disease in the regional lymph nodes. Combined TME and preoperative radiotherapy has become a very effective therapeutic concept in rectal cancer, resulting in a low local recurrence rate and improved survival [30, 31]. In Japan, extended lateral lymph node dissection is a surgical procedure which resects macroscopic and microscopic local metastases. This procedure therefore has a potentially similar local control effect to adjuvant radiotherapy. Watanabe et al. [32] suggested that preoperative radiotherapy could be an alternative to extended lateral lymph node dissection. In the retrospective study, 115 rectal cancer patients were divided into two groups, and there was no difference between the group with radiotherapy (without lateral lymph node dissection) and the group with lateral lymph node dissection (without radiotherapy) in terms of recurrence rate and survival. A randomized controlled trial of lateral lymph node dissection versus nerve-preserving resection for rectal cancer after preoperative radiotherapy showed that there was no difference in the postoperative survival of patients who had systematic lateral dissection and those who did not [33]. This study also suggested that lateral node dissection is not necessary in terms of curability for patients with advanced rectal cancer who undergo preoperative radiotherapy. These studies suggested that the degree to which preoperative radiotherapy reduces the risk of recurrence is equivalent to that of lateral dissection, which can result in urinary and male sexual dysfunction.

Adjuvant Chemotherapy for Systemic Control

Despite the current quality of surgical procedures, locoregional treatment is limited as advanced primary rectal cancer may be associated with systemic spread of disease and distant metastases. The role of systemic adjuvant chemotherapy is therefore to obtain further improvement in survival. Although the role of systemic adjuvant chemotherapy in colon cancer patients with lymph node involvement has been established in a large number of clinical trials, rectal cancer differs from colon cancer in that there is an increased risk of local recurrence. The optimal adjuvant therapy for patients with rectal cancer has been combined systemic chemotherapy and radiotherapy, especially in the Western world. However, current practices of adjuvant therapy differ between countries and even between institutions within the same country. In Japan, several reports have demonstrated the usefulness of oral uracil-tegafur for adjuvant chemotherapy in colorectal cancer patients [34, 35]. Since oral chemotherapeutic agents such as uracil-tegafur are advantageous due to their ease of administration, patient con-

venience and lack of need for catheterization, they have been widely used in Japan. Recently, adjuvant chemotherapy with uracil-tegafur was shown to improve survival of patients with stage III rectal cancer after standardized mesorectal excision with selective lateral lymph node dissection [36].

Conclusion

In the Japanese Guideline 2005 for Colorectal Cancer, the criteria for lateral lymph node dissection is lower-lying (below peritoneal reflection) and locally advanced (>T2) rectal cancer. It is still unclear which procedure is superior, lateral lymph node dissection or TME. The randomized controlled trial of lateral lymph node dissection versus TME for rectal cancer of the Japan Clinical Oncology Group (JCOG0212 trial, <http://www.jcog.jp/>) is currently underway, and the results are eagerly awaited. Retrospectively, both TME and lateral lymph node dissection for lower rectal cancer have achieved good local control, although the morbidity profiles are different. With the introduction of TME as a standardized, precise surgical technique, very low local recurrence rates have been reported by individual institutions [4, 8, 9] and surgeon-related variability has been minimal. Havenga et al. [37] analyzed 691 patients with rectal cancer from three centers in the United States, Europe, and Japan and demonstrated similar survival and local recurrence rates in each. With today's standardized surgeon skill, low rates of local recurrence should be achieved with both TME and lateral lymph node dissection. However, there are limitations to these locoregional treatments, and adjuvant therapy is needed to prolong survival further. In addition, the individual preferences or medical conditions of the patient may play an important role in the choice of a particular treatment. For example, as the reduction in the rate of recurrence following lateral lymph node dissection is equivalent to that of radiotherapy, lateral dissection would be indicated in patients for whom radiotherapy is contraindicated.

By combining optimal surgical technique with appropriate surgical decision making, the surgeon can provide the patient with resectable rectal cancer the best chance of avoiding local recurrence, improved QOL, and ultimately, improved survival. In the future, molecular predictors of response to preoperative radiotherapy or sentinel lymph node mapping may facilitate further individualization, which will help to guide clinical decision making as well as identifying the best modality to use.

References

- 1 Glimelius B, Isacson U, Jung B, Pahlman L: Radiotherapy in addition to radical surgery in rectal cancer. *Acta Oncol* 1995;34:565-570.
- 2 Gastrointestinal Tumor Study Group: Adjuvant therapy of colon cancer: results of a prospectively randomized trial. *N Engl J Med* 1984;310:737-743.
- 3 Heald RJ, Husband EM, Ryall RD: The mesorectum in rectal cancer surgery - the clue to pelvic recurrence? *Br J Surg* 1982;69:613-616.
- 4 Heald RJ, Ryall RD: Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;i:1479-1482.
- 5 Miles WE: A method of performing abdomino-peritoneal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. *Lancet* 1908;ii:1812-1813.
- 6 Williams NS, Durdley P, Johnston D: The outcome following sphincter-saving resection and abdominoperineal resection for low rectal cancer. *Br J Surg* 1985;72:595-598.
- 7 Pollett WG, Nicholls RJ: The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum. *Ann Surg* 1983;198:159-163.
- 8 MacFarlane JK, Ryall RD, Heald RJ: Mesorectal excision for rectal cancer. *Lancet* 1993;341:457-60.
- 9 Enker WE: Potency, cure, and local control in the operative treatment of rectal cancer. *Arch Surg* 1992;127:1396-1401.
- 10 Lowry AC, Simmang CL, Boulos P, Farmer KC, Finan PJ, Hyman N, Killingback M, Lubowski DZ, Moore R, Penfold C, Savoca P, Stitz R, Tjandra JJ: Consensus statement of definitions for anorectal physiology and rectal cancer: report of the Tripartite Consensus Conference on Definitions for Anorectal Physiology and Rectal Cancer, Washington, DC, May 1, 1999. *Dis Colon Rectum* 2001;44:915-919.
- 11 Morikawa E, Yasutomi M, Shindou K, Matsuda T, Mori N, Hida J, Kubo R, Kitaoka M, Nakamura M, Fujimoto K, et al: Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method. *Dis Colon Rectum* 1994;37:219-223.
- 12 Hida J, Yasutomi M, Fujimoto K, Maruyama T, Okuno K, Shindo K: Does lateral lymph node dissection improve survival in rectal carcinoma? Examination of node metastases by the clearing method. *J Am Coll Surg* 1997;184:475-480.
- 13 Yamakoshi H, Ike H, Oki S, Hara M, Shimada H: Metastasis of rectal cancer to lymph nodes and tissues around the autonomic nerves spared for urinary and sexual function. *Dis Colon Rectum* 1997;40:1079-1084.
- 14 Moriya Y, Sugihara K, Akasu T, Fujita S: Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. *World J Surg* 1997;21:728-732.
- 15 Takahashi T, Ueno M, Azekura K, Ohta H: Lateral node dissection and total mesorectal excision for rectal cancer. *Dis Colon Rectum* 2000;43:S59-S68.
- 16 Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T: Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. *Br J Surg* 2005;92:756-763.
- 17 Morita T, Murata A, Koyama M, Totsuka E, Sasaki M: Current status of autonomic nerve-preserving surgery for mid and lower rectal cancers: Japanese experience with lateral node dissection. *Dis Colon Rectum* 2003;46:S78-S87.
- 18 Fujita S, Yamamoto S, Akasu T, Moriya Y: Lateral pelvic lymph node dissection for advanced lower rectal cancer. *Br J Surg* 2003;90:1580-1585.
- 19 Hojo K, Koyama Y, Moriya Y: Lymphatic spread and its prognostic value in patients with rectal cancer. *Am J Surg* 1982;144:350-354.
- 20 Mori T, Takahashi K, Yasuno M: Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal cancer surgery and its results: the impact of lateral lymph node dissection. *Langenbecks Arch Surg* 1998;383:409-415.
- 21 Hojo K, Sawada T, Moriya Y: An analysis of survival and voiding, sexual function after wide iliopelvic lymphadenectomy in patients with carcinoma of the rectum, compared with conventional lymphadenectomy. *Dis Colon Rectum* 1989;32:128-133.
- 22 Fengler SA, Pearl RK: Technical considerations in the surgical treatment of colon and rectal cancer. *Semin Surg Oncol* 1994;10:200-207.
- 23 Bruch HP, Schwandner O, Schiedeck TH, Roblick UJ: Actual standards and controversies on operative technique and lymph-node dissection in colorectal cancer. *Langenbecks Arch Surg* 1999;384:167-175.
- 24 Sugihara K, Moriya Y, Akasu T, Fujita S: Pelvic autonomic nerve preservation for patients with rectal carcinoma. *Oncologic and functional outcome. Cancer* 1996;78:1871-1880.
- 25 Maeda K, Maruta M, Utsumi T, Sato H, Toyama K, Matsuoka H: Bladder and male sexual functions after autonomic nerve-sparing TME with or without lateral node dissection for rectal cancer. *Tech Coloproctol* 2003;7:29-33.
- 26 Ueno H, Mochizuki H, Hashiguchi Y, Hase K: Prognostic determinants of patients with lateral nodal involvement by rectal cancer. *Ann Surg* 2001;234:190-197.
- 27 Ueno H, Mochizuki H, Shinto E, Hashiguchi Y, Hase K, Talbot IC: Histologic indices in biopsy specimens for estimating the probability of extended local spread in patients with rectal carcinoma. *Cancer* 2002;94:2882-2891.
- 28 Ueno H, Mochizuki H, Fujimoto H, Hase K, Ichikura T: Autonomic nerve plexus involvement and prognosis in patients with rectal cancer. *Br J Surg* 2000;87:92-96.
- 29 Matsumoto T, Ohue M, Sekimoto M, Yamamoto H, Ikeda M, Monden M: Feasibility of autonomic nerve-preserving surgery for advanced rectal cancer based on analysis of micrometastases. *Br J Surg* 2005;92:1444-1448.
- 30 Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ: Dutch Colorectal Cancer Group: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638-646.
- 31 Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R; German Rectal Cancer Study Group: Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731-1740.
- 32 Watanabe T, Tsurita G, Muto T, Sawada T, Sunouchi K, Higuchi Y, Komuro Y, Kanazawa T, Iijima T, Miyaki M, Nagawa H: Extended lymphadenectomy and preoperative radiotherapy for lower rectal cancers. *Surgery* 2002;132:27-33.
- 33 Nagawa H, Muto T, Sunouchi K, Higuchi Y, Tsurita G, Watanabe T, Sawada T: Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum* 2001;44:1274-1280.
- 34 Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, Takagi H, Nimura Y, Hasumi A, Baba S, Manabe T, Maruta M, Miura K, Yamaguchi A: Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. *Langenbecks Arch Surg* 2002;386:575-581.
- 35 Kusunoki M, Yanagi H, Kotera H, Noda M, Yamamura T: Effects of pharmacokinetic modulating chemotherapy using oral UFT and continuous venous 5FU infusion on the prognosis of irradiated rectal carcinomas with p53 overexpression. *Int J Oncol* 1998;13:653-657.
- 36 Akasu T, Moriya Y, Ohashi Y, Yoshida S, Shirao K, Kodaira S; National Surgical Adjuvant Study of Colorectal Cancer: Adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial. *Jpn J Clin Oncol* 2006;36:237-244.
- 37 Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC, van de Velde CJ: Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1,411 patients. *Eur J Surg Oncol* 1999;25:368-374.

Surgical Treatment for Liver Cancer

Current Issues

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Key Words

Liver cancer • Hepatocellular carcinoma • Hepatectomy •
Portal vein embolization • Hepatic resection

Abstract

Surgical treatment of hepatocellular carcinoma (HCC) has developed remarkable for several reasons. The surgical mortality rates of patients with HCC after hepatectomy have decreased due to appropriate criteria for surgery, refined surgical techniques and improvement in the pre- and post-operative management. In preoperative management, refinements in liver function tests and strategies for esophageal varices, and the induction of preoperative portal vein embolization have contributed favorably to the outcome after hepatectomy for HCC. Furthermore, hepatectomy has been technically refined by various vascular control methods and liver transection devices based on the realization that surgical anatomical information also plays a major role in improving surgical outcome. Also concomitant splenectomy with hepatectomy might extend the criteria for surgery in HCC patients with hypersplenism. Therefore, hepatectomy is a safe therapeutic approach that could bring about a favorable outcome in patients with HCC. Nowadays transplantation is one of the therapeutic options for HCC pa-

tients, even in Japan. Herein the surgical treatment of HCC in Japan is reviewed and current issues in the surgical treatment of HCC are discussed.

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Introduction

Surgical treatment of hepatocellular carcinoma (HCC) has remarkably improved for several reasons. The surgical mortality rates of HCC patients have decreased after hepatectomy due to the appropriate criteria for surgery, refined surgical techniques, and improvement in pre- and postoperative management. Therefore, hepatectomy has become a safe therapeutic approach that could bring about a favorable outcome for HCC patients. Herein, the surgical treatment of HCC in Japan is reviewed, and current issues in the surgical treatment of HCC are described.

Preoperative Management

Evaluation of Liver Function

In Japan 90% of HCC patients have chronic liver dysfunction due to hepatitis B or C virus infection [1]. There-

fore, preoperative evaluation of liver function is very important to decide the surgical indication in HCC patients and to perform surgery safely. Several hepatic function tests have been developed and were applied to patients in the 1980s and 1990s. At present the most frequently used assessments are the Child-Pugh classification and indocyanine green (ICG) test. Other tests, such as blood coagulation factors (partial thromboplastin time, hepaplastin test, etc.), galactose elimination capacity, and asialoscintigraphy, are also useful as additional functional tests. However, the ICG test cannot evaluate liver function correctly in patients with obstructive jaundice. In such cases, the galactose elimination capacity and blood coagulation factors could be useful parameters. Obstructive jaundice is seldom found in HCC patients, but is usually encountered in patients with intrahepatic cholangiocarcinoma because it often involves the hilar bile duct and induces obstructive jaundice.

Recently, patients with HCC and liver cirrhosis have been classified according to newly proposed score systems such as the Cancer of the Liver Italian Program (CLIP) score [2] and Japan Integrated Staging (JIP) score [3]. These scoring systems are related to both tumor stage and liver function. Although the CLIP scoring system has been well validated by many authors [4–6] in terms of its prognostic value in HCC patients, this scoring system has some problems and limitations when applied to patients with early-stage HCC. Therefore, a new staging system based on the Liver Cancer Study Group of Japan, the JIS score has been proposed in Japan [3]. This staging system combined the Child-Pugh grade and TNM staging. Further reevaluation of these staging systems must be done.

Preoperative Portal Vein Embolization

Portal vein embolization, developed by Makuuchi et al. [7] and Kinoshita et al. [8], has also been applied not only to patients with obstructive jaundice but also to cirrhotic patients with HCC. Kinoshita et al. [8] and Abdalla et al. [9] have shown the usefulness of portal vein embolization in patients with liver cirrhosis undergoing major hepatectomy. Embolization could be indicated in patients undergoing major hepatectomy when the estimated liver volume after hepatectomy is not enough to tolerate surgery. A recent report [10] has shown that sequential transarterial chemoembolization and portal vein embolization before surgery increase the rate of hypertrophy of the future remnant liver volume and lead to a higher rate of complete tumor necrosis associated with a longer recurrence-free survival. Furthermore, preoperative portal vein embolization might bring about the

benefit of avoiding intraportal venous tumor spreading into the liver during operation. Portal vein embolization before hepatectomy for HCC might have beneficial effects not only on liver functional capacity, but also on oncological control.

Splenectomy

Most patients with HCC have a cirrhotic liver, and some of them have concomitant hypersplenism and portal hypertension. It is still controversial whether HCC patients with thrombocytopenia should undergo surgical resection or not if liver function is tolerable enough for them to have hepatectomy. Splenectomy has been advocated for patients with HCC and thrombocytopenia prior to hepatectomy or synchronously. Sugawara et al. [11] reported that splenectomy can increase the safety of hepatectomy in selected patients with HCC by reducing both the likelihood of bleeding complications and bilirubin overload. Chen et al. [12] also reported that simultaneous hepatectomy and splenectomy is associated with an improved 5-year tumor-free survival in patients with HCC and hypersplenism. Therefore, patients with HCC and hypersplenism should not be considered irresectable only due to thrombocytopenia.

Strategy for Esophageal Varices

If the HCC patient has esophageal varices that could rupture, preoperative endoscopic treatments such as variceal ligation and sclerotherapy should be performed to avoid postoperative bleeding after hepatectomy [13, 14]. Partial splenic embolization has also been done preoperatively for patients with HCC, especially when accompanied by thrombocytopenia [15, 16]. During hepatic resection for HCC, the Hassab operation and splenectomy might be performed concomitantly aiming to control esophageal varices and thrombocytopenia more effectively [17, 18].

Operative Procedures

Surgical resection for HCC should be done by anatomical hepatectomy according to the inflowing vessels at the sub-segment level such as segments II, V, etc., according to Couinaud's classification. Systemized hepatectomy with Glisson's pedicle transection at the hepatic hilus has commonly been utilized in hepatectomy for small HCC in cirrhotic patients (fig. 1, 2). Anatomical resection has been considered beneficial for complete segmental resection of the cancer burden and the non-valid

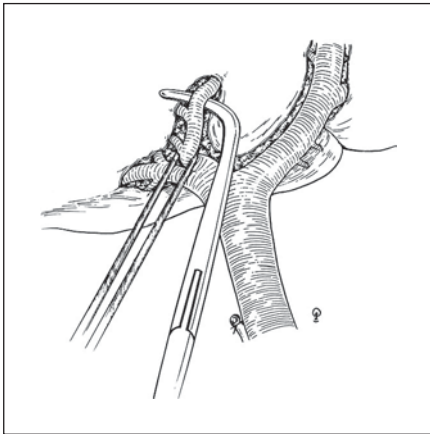


Fig. 1. Segment VIII hepatectomy by systematic Glisson's pedicle transection at the hepatic hilus.

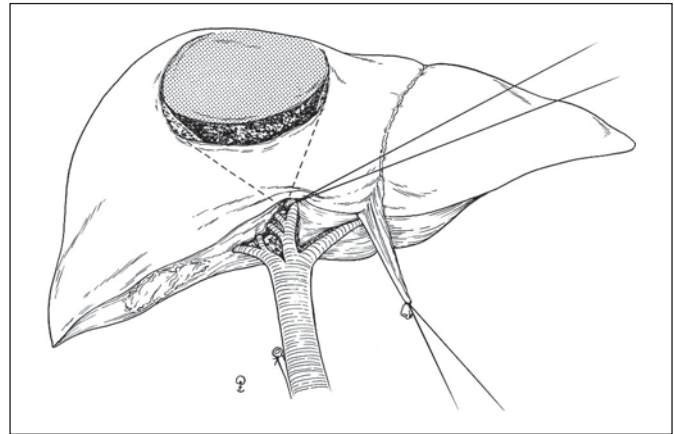


Fig. 2. Segment VIII hepatectomy; parenchymal transection following Glisson's pedicle ligation at the hepatic hilus.

hepatic parenchyma. While during transection of the hepatic parenchyma both Pringle's maneuver and hemivascular clamp have commonly been utilized to reduce intraoperative blood loss, no obvious differences in liver damage, blood loss and operative time have been found between the two vascular control methods [19–22]. Several mechanical devices, such as CUSA, Bipolar electrocautery, Water-Jet, Microwave Coagulator and Tissue Link, etc., have independently been applied during liver parenchymal transection in various institutions. However, there is still no clear evidence showing which of the devices is significantly better than the others [19, 23–26].

In the case of advanced HCC involving the inferior vena cava (IVC) with intravenous tumor thrombus, total hepatic vascular exclusion in the abdominal space should be required for excision of the tumor thrombus from the IVC without massive blood loss [27]. The cirrhotic liver with Child's A and B liver function can tolerate ischemic liver damage over a duration of 30 min. The excision of the tumor thrombus from the IVC commonly takes less than 30 min because HCC seldom directly invades the IVC wall, and therefore reconstruction of the IVC using a graft is usually not required after tumor thrombectomy from the IVC. However, if the tumor thrombus of the IVC extends into the suprarenic IVC or the right atrium, vascular control at the level of intrathoracic IVC or cardiopulmonary bypass should be required for removal of the intravascular tumor thrombus (fig. 3, 4). There have been some case reports with long-term survivors following these aggressive surgical approaches, despite advanced HCC with extensive intravascular tumor throm-

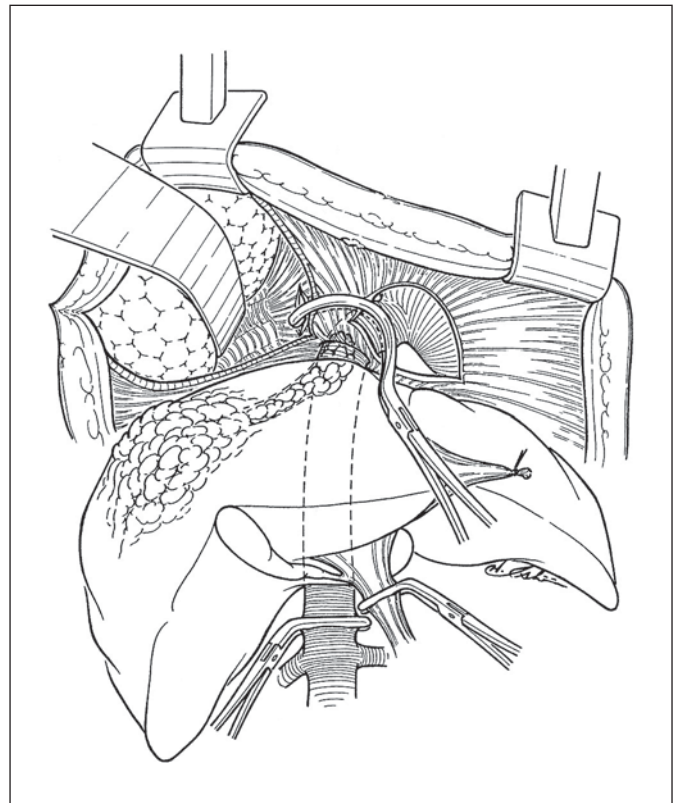


Fig. 3. Total hepatic vascular exclusion for HCC with tumor thrombus extending into the inferior vena cava at the intra-thoracic level.

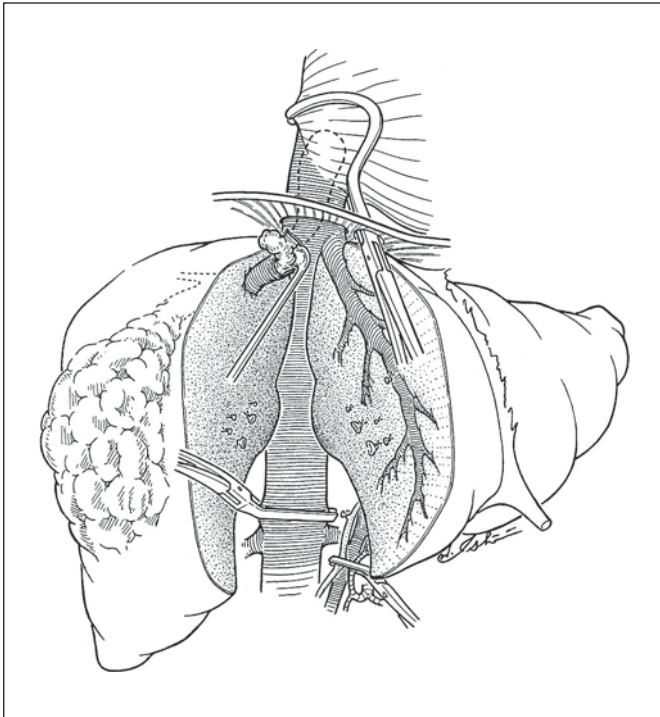


Fig. 4. Hepatectomy for HCC with tumor thrombus extending into the intra-thoracic inferior vena cava under total hepatic vascular exclusion and tumor thrombectomy from the inferior vena cava.

bus [28, 29]. Recently, Sakon et al. [30] reported that interferon may have remarkable effects on irresectable HCC with an intravascular tumor thrombus. At present a prospective clinical trial is in progress to clarify the effect of interferon.

Postoperative Complications and Managements

Many institutions have reported that postoperative liver failure very rarely occurs after hepatectomy [31–35]. The decrease in the incidence of postoperative liver failure might be due to appropriate patient selection by excellent evaluation and well-defined criteria for liver functional reserve, and the improvement in surgical technique. Therefore, hepatic resection for HCC has been done without blood transfusion in most patients. The criteria of Imamura et al. [36], using the ICG test, is very popular and easily available to judge the surgical indication of hepatectomy in cirrhotic patients with HCC. Besides liver failure, there are many other postoperative complications such as pleural effusion, biliary fistula, bi-

loma, abdominal abscess, etc. However, hospital stay after surgery has been shortened without major complications. Therefore, at present the surgical mortality is reported to be less than 1% in most institutions in Japan.

Survival after Operation

Survival after surgical resection has improved remarkably with the recent progress in surgical skills and the use of appropriate indication criteria. Therefore, the surgical mortality rate has decreased to less than 2% as shown by recent reports. However, in 1980 the Liver Cancer Study Group of Japan reported a high surgical mortality rate of 27% in the patients with HCC [37]. The major cause of this high surgical mortality was hepatic failure. Several liver function tests, such as the ICG retention test, asialoscintigraphy, and galactose elimination capacity, could correctly evaluate the preoperative functional reserve of the liver in cirrhotic patients with HCC. Experience with a large number of patients undergoing surgical resection could contribute to the development of appropriate selection criteria in cirrhotic patients by analyzing the surgical outcome retrospectively. The 5-year survival after surgical resection in HCC patients increased from 12 to 55% between 1980 and 2005 in Japan [1]. Recently liver transplantation was performed as a new form of surgical treatment for HCC. In Japan the number of the patients who underwent liver transplantation for HCC greatly increased after 2005 [1]. A follow-up survey of primary liver cancer in Japan in 2005 reported that survival rates in HCC patients were 88, 71, 55, and 29% at 1, 3, 5, and 10 years after surgical resection, respectively [1].

Strategy for Recurrence

One third of the HCC patients who underwent surgical resection have been reported to have recurrence. Transcatheter arterial embolization and local ablation therapy have been utilized mainly for the recurrence of HCC in the liver. However, a small number of the recurrent patients were able to undergo repeat hepatectomy, which resulted in a favorable outcome [38, 39]. Of course liver transplantation has also been performed in strictly selected patients with recurrence of HCC only in the liver [40–42]. Further studies need to be done to clarify the implications of aggressive surgical treatment for recurrent HCC, such as repeat hepatectomy and liver transplantation.

Conclusion

Surgical resection for HCC in the liver has been defined as a safe and effective treatment. Therefore, surgical resection should be considered the first-line therapy for

HCC patients, even cirrhotic patients, and appropriate liver function tests and indication criteria should be used to evaluate whether the patients are able to tolerate surgery.

References

- Ikai I, Arii S, Ichida T, Okita K, Omata M, Kojiro M, Takayasu K, Nakanuma Y, Makuuchi M, Matsuyama Y, Yamaoka Y: Report of the 16th follow-up survey of primary liver cancer. *Hepatol Res* 2006;32:163–172.
- A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998; 28:751–755.
- Kudo M, Chung H, Osaki Y: Prognostic staining system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). *J Gastroenterol* 2003;38:207–215.
- Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology* 2000;31:840–845.
- Levy I, Sherman M; Liver Cancer Study Group of the University of Toronto: Staging of hepatocellular carcinoma: assessment of the CLIP, Okuda, and Child-Pugh staging systems in a cohort of 257 patients in Toronto. *Gut* 2002;50:881–885.
- Llovet JM, Bruix J: Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. *Hepatology* 2000;32:679–680.
- Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, Yamazaki S, Hasegawa H, Ozaki H: Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery* 1990;5:521–527.
- Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S: Preoperative portal vein embolization for hepatocellular carcinoma. *World J Surg* 1986;10:803–808.
- Abdalla EK, Hicks ME, Vauthey JN: Portal vein embolization: rationale, technique and future prospects. *Br J Surg* 2001;88:165–175.
- Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V: Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. *Br J Surg* 2006;93:1091–1098.
- Sugawara Y, Yamamoto J, Shimada K, Yamasaki S, Kosuge T, Takayama T, Makuuchi M: Splenectomy in patients with hepatocellular carcinoma and hypersplenism. *J Am Coll Surg* 2000;190:446–450.
- Chen XP, Huang WZY, Qiu FZ: Use of hepatectomy and splenectomy to treat hepatocellular carcinoma with cirrhotic hypersplenism. *Br J Surg* 2005;92:334–339.
- Amitrano L, Guardascione MA, Bennato R, Manguso F, Balzano A: MELD score and hepatocellular carcinoma identify patients at different risk of short-term mortality among cirrhotics bleeding from esophageal varices. *J Hepatol* 2005;42:820–825.
- Lang BH, Poon RT, Fan ST, Wong J: Outcomes of patients with hepatocellular carcinoma presenting with variceal bleeding. *Am J Gastroenterol* 2004;99:2158–2165.
- Sangro B, Bilbao I, Herrero I, Corella C, Longo J, Beloqui O, Ruiz J, Zozaya JM, Quiruga J, Prieto J: Partial splenic embolization for the treatment of hypersplenism in cirrhosis. *Hepatology* 1993;18:309–314.
- Wu FS, Zhao WH, Liang TB, Ma ZM, Teng LS, Wang M, Zheng SS: Survival factors after resection of small hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2005;4:379–384.
- Yamamoto S, Sato Y, Takeishi T, Hirano K, Koabayashi T, Watanabe T, Hatakeyama K: Successful surgical treatment for hepatocellular carcinoma and concomitant risky esophageal varices. *Hepatogastroenterology* 2005;52:1083–1086.
- Li H, Hu YL, Wang Y, Zhang DS, Jiang FX: Simultaneous operative treatment of patients with primary liver cancer associated with portal hypertension. *Hepatobiliary Pancreat Dis Int* 2002;1:92–93.
- Lesurtel M, Selzner M, Petrowsky H, McCormack L, Clavien PA: How should transection of the liver be performed? A prospective randomized study in 100 consecutive patients: comparing four different transection strategies. *Ann Surg* 2005;242:814–823.
- Chau GY, Lui WY, King KL, Wu CW: Evaluation of effect of hemihepatic vascular occlusion and the Pringle maneuver during hepatic resection for patients with hepatocellular carcinoma and impaired liver function. *World J Surg* 2005;29:1374–1383.
- Dixon E, Vollmer CM Jr, Bathe OF, Sutherland F: Vascular occlusion to decrease blood loss during hepatic resection. *Am J Surg* 2005;190:75–86.
- Figueras J, Liado L, Ruiz D, Ramos E, Busquets J, Rafecas A, Torras J, Fabregat J: Complete versus selective portal triad clamping for minor liver resections: a prospective randomized trial. *Ann Surg* 2005;241:582–590.
- Nascimento M, Abourjeily N, Ghosh A, Zhang WW, Matlashewski G: Heterologous expression of a mammalian protein tyrosine phosphatase gene in *Leishmania*: effect on differentiation. *Hepatogastroenterology* 2003;50:1517–1520.
- Rau HG, Buttler ER, Baretton G, Schardey HM, Schildberg FW: Jet-cutting supported by high frequency current: new technique for hepatic surgery. *World J Surg* 1997;21: 254–260.
- Rau HG, Schardey HM, Buttler E, Reuter C, Cohnert TU, Schildberg FW: A comparison of different techniques for liver resection: blunt dissection, ultrasonic aspirator and jet-cutter. *Eur J Surg Oncol* 1995;21:183–187.
- Saiura A, Yamamoto J, Koga R, Sakamoto Y, Kokudo N, Seki M, Yamaguchi T, Yamaguchi T, Muto T, Makuuchi M: Usefulness of LigaSure for liver resection: analysis by randomized clinical trial. *Am J Surg* 2006;192: 41–45.
- Miyazaki M, Ito H, Nakagawa K, Ambiru S, Simizu H, Okuno A, Nukui Y, Yoshitomi H, Kusashio K, Furuya S, Nakajima N: Aggressive surgical resection for hepatic metastases involving the inferior vena cava. *Am J Surg* 1999;177:294–298.
- Kashima Y, Miyazaki M, Ito H, Kaiho T, Nakagawa K, Ambiru S, Shimizu H, Futuya S, Nakajima N: Effective hepatic artery chemoembolization for advanced hepatocellular carcinoma with extensive tumour thrombus through the hepatic vein. *J Gastroenterol Hepatol* 1999;14:922–927.
- Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, Shimizu Y, Ohtuska M, Togawa A, Kimura F: An approach to intrapericardial inferior vena cava through the abdominal cavity, without median sternotomy, for total hepatic vascular exclusion. *Hepatogastroenterology* 2001;48:1443–1446.

- 30 Sakon M, Nagano H, Dono K, Nakamori S, Umeshita K, Yamada A, Kawata S, Imai Y, Lijima S, Monden M: Combined intraarterial 5-fluorouracil and subcutaneous interferon-alpha therapy for advanced hepatocellular carcinoma with tumor thrombi in the major portal branches. *Cancer* 2002;94:435-442.
- 31 Cucchetti A, Ercolani G, Cescon M, Ravaoli M, Zanello M, Del Gaudio M, Lauro A, Vivarelli M, Luca Grazi G, Pinna AD: Recovery from liver failure after hepatectomy for hepatocellular carcinoma in cirrhosis: meaning of the model for end-stage liver disease. *J Am Coll Surg* 2006;203:670-676.
- 32 Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC: Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006;243:373-379.
- 33 Blazan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, Durand F: The '50-50 criteria' on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 2005;242:824-829.
- 34 Maeda Y, Nishida M, Takao T, Tamesa T, Tangoku A, Oka M: Risk factors for postoperative liver failure after hepatectomy for hepatocellular carcinoma. *Hepatogastroenterology* 2004;51:1792-1796.
- 35 Fan ST, Lai EC, Lo CM, Ng IO, Wong J: Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995;130:198-203.
- 36 Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M: Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. *J Hepatobiliary Pancreat Surg* 2005;12:16-22.
- 37 Okuda K; the Liver Cancer Study Group of Japan: Primary liver cancers in Japan. *Cancer* 1980;45:2663-2669.
- 38 Shimada M, Takenaka K, Taguchi K, Fujiwara Y, Gion T, Kajiyama K, Maeda T, Shirabe K, Yanaga K, Sugimachi K: Prognostic factors after repeat hepatectomy for recurrent hepatocellular carcinoma. *Ann Surg* 1998;227:80-85.
- 39 Nagasue N, Kohno H, Hayashi T, Uchida M, Ono T, Yukaya H, Yamanoi A: Repeat hepatectomy for recurrent hepatocellular carcinoma. *Br J Surg* 1996;83:127-131.
- 40 Prak JW, Lee KW, Kim SJ, Choi SH, Heo JS, Kwon CH, Kim DJ, Han YS, Lee SK, Joh JW: Outcome of patients with recurrent hepatocellular carcinoma in liver transplantation. *Transplant Proc* 2006;38:2121-2122.
- 41 Grasso A, Stigliano R, Morisco F, Martines H, Quaglia A, Dhillon AP, Patch D, Davidson BR, Rollets K, Burroughs AK: Liver transplantation and recurrent hepatocellular carcinoma: predictive value of nodule size in a retrospective and explant study. *Transplantation* 2006;81:1532-1541.
- 42 Yokoi H, Isaji S, Yamagiwa K, Tabata M, Nemoto A, Sakurai H, Usui M, Uemoto S: The role of living-donor liver transplantation in surgical treatment for hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2006;13:123-130.

Liver Transplantation for Hepatocellular Carcinoma

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Key Words

Hepatocellular carcinoma · Liver transplantation · Milan criteria

Abstract

Hepatocellular carcinoma (HCC) has been a major reason for liver transplantation (LT). Globally, LT for HCC is performed on the basis of the Milan criteria, and if performed within those criteria, then the outcome is not different from that of LT performed for other primary diseases. On the other hand, the scope of the Milan criteria covers only early-stage HCC, and many HCC patients do not meet the criteria even at the time of diagnosis. Therefore, over the last decade, efforts have been made to perform LT for patients whose clinical characteristics lie outside the Milan criteria. In Japan, more than 99% of LTs are living donor LTs (LDLTs) and more than 15% of LTs are performed in patients with HCC. The 1- and 3-year actual survival rates of LDLT for HCC in Japan are 82 and 79%, respectively. Efforts to extend the Milan criteria have also been made in Japan. To improve the outcome of LT for HCC, pre- and postoperative management of hepatitis B and hepatitis C, and immunosuppressant specific for this type of LT are still crucial issues. In this review, we provide an overview of current outcome, efforts to extend the Milan criteria, control of viral hepatitis, and immunosuppression for LT in patients with HCC.

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Introduction

Because of the shortage of donor organs and the need for sustained immunosuppression after transplantation, as therapy for malignant disease transplantation is contraindicated for most organs other than the liver. It is not surprising that liver transplantation (LT) can be regarded as an optimal therapeutic modality for hepatocellular carcinoma (HCC), because, as well as radically removing the whole tumor, LT also replaces cirrhotic liver with healthy liver. Until recently, however, the outcome of LT for HCC remained poor.

Only experimental LTs were studied using animal models before 1960. Starzl and Putnam [1] were the first to attempt human LT in 1963, but the first successful LT was not achieved until 1967. From the dawn of clinical LT, HCC was a major target for LT, but accumulated evidence indicated that although LT gave good results in the short term, cancer recurred in the vast majority of patients within 2 years [2]. Over the following two decades, the outcome of LT improved dramatically, and in 1983 the National Institutes of Health approved LT as a valid therapy for end-stage liver disease. However, the outcome of LT for HCC still remained poor, with a 5-year survival rate of only 18% [3], until the Milan criteria were proposed in 1996 [4].

Table 1. Actual survival rate after LT

| Reference | Survival rate, %, at | | | |
|-----------------------|----------------------|---------|---------|---------|
| | 1 year | 3 years | 4 years | 5 years |
| Mazzaferro et al. [4] | | | | |
| Milan | – | – | 85 | – |
| Exceeding Milan | – | – | 50 | – |
| Zavaglia et al. [5] | | | | |
| Milan | – | 76 | – | 74 |
| Exceeding Milan | – | 73 | – | 55 |
| Llovet et al. [6] | | | | |
| Milan | 82 | 69 | – | 69 |
| Exceeding Milan | – | – | – | – |
| Todo et al. [8] | | | | |
| Milan | 81 | 79 | – | – |
| Exceeding Milan | 75 | 60 | – | – |

Table 2. Recurrence-free survival rate after LT

| Reference | Recurrence-free survival rate, %, at | | | |
|-----------------------|--------------------------------------|---------|---------|---------|
| | 1 year | 3 years | 4 years | 5 years |
| Mazzaferro et al. [4] | | | | |
| Milan | – | – | 92 | – |
| Exceeding Milan | – | – | 59 | – |
| Zavaglia et al. [5] | | | | |
| Milan | 95 | 92 | – | 91 |
| Exceeding Milan | – | – | – | – |
| Llovet et al. [6] | | | | |
| Milan | 100 | 99 | – | 98 |
| Exceeding Milan | – | – | – | – |
| Todo et al. [8] | | | | |
| Milan | 82 | 79 | – | – |
| Exceeding Milan | 65 | 53 | – | – |

After 1996, many countries adopted the Milan criteria for LT, and outcomes subsequently improved. As the Milan criteria are based on cadaveric LT, there has been some concern about applying the criteria to living donor LT (LDLT). In the meantime, there have been efforts to perform LT in patients whose clinical characteristics lie outside the Milan criteria.

In this review, we provide an overview of the current status and problems of LT for HCC in Japan, and also worldwide.

Milan Criteria

In 1996, Mazzaferro et al. [4] reported their experience with LT for HCCs. In their series, the outcome of LT in patients with HCC who fulfilled the Milan criteria (a single tumor ≤ 5 cm or not more than 3 lesions, none exceeding 3 cm in greatest diameter, without portal invasion and distant metastases) was not different from that of patients without HCC. The 4-year and recurrence-free survival rates in patients who fulfilled and did not fulfill the Milan criteria were 85 and 92%, and 50 and 59%, respectively. Recent studies have reported 5-year survival rates of 70–80% and recurrence rates of about 10% [5, 6]. Actual and recurrence-free survival rates are shown in tables 1 and 2.

In the United States, the Organ Procurement and Transplantation Network (OPTN) adopted and modified the Milan criteria, and currently only patients who meet the modified criteria (1 lesion 2–5 cm, or 2–3 lesions each

≤ 3 cm) are enrolled on the waiting list. Enrolled patients are allocated a Model of End-stage Liver Disease (MELD) score and prioritized on the LT waiting list. The MELD score is a numerical score ranging from 6 to 40, and indicates how urgently a patient should undergo LT within the next 3 months. The MELD score is calculated from the serum bilirubin level, prothrombin time international normalized ratio, and serum creatinine level [7].

LDLT is by far the major LT procedure in Japan, where the Milan criteria have also been adopted. Large-scale clinical outcomes of LDLTs for HCCs were reported by Todo et al. [8] in 2004. In their report, the overall 1- and 3-year patient survival rates were 78.1 and 69.0%, respectively. The 3-year survival and disease-free survival rates in patients with HCC who fulfilled the Milan criteria were 78.7 and 79.1%, respectively, and those of patients who did not fulfill the criteria were 60.4 and 52.6%, respectively (fig. 1). Forty of 316 patients (13%) developed HCC recurrence. Multivariate analyses indicated that the pretransplant serum AFP level (>20 ng/ml), tumor size (>2 cm), portal invasion, and bilobar tumor distribution were independent risk factors for recurrence [8]. Of the 316 patients, 138 (43.7%) fulfilled the Milan criteria and 171 (54.1%) did not.

Current Status of LT in Japan

The Japanese Liver Transplantation Society [9] released data on the outcome of LT for HCC in 2005. By December 2004, 3,246 LTs had been performed at 52 transplant cen-

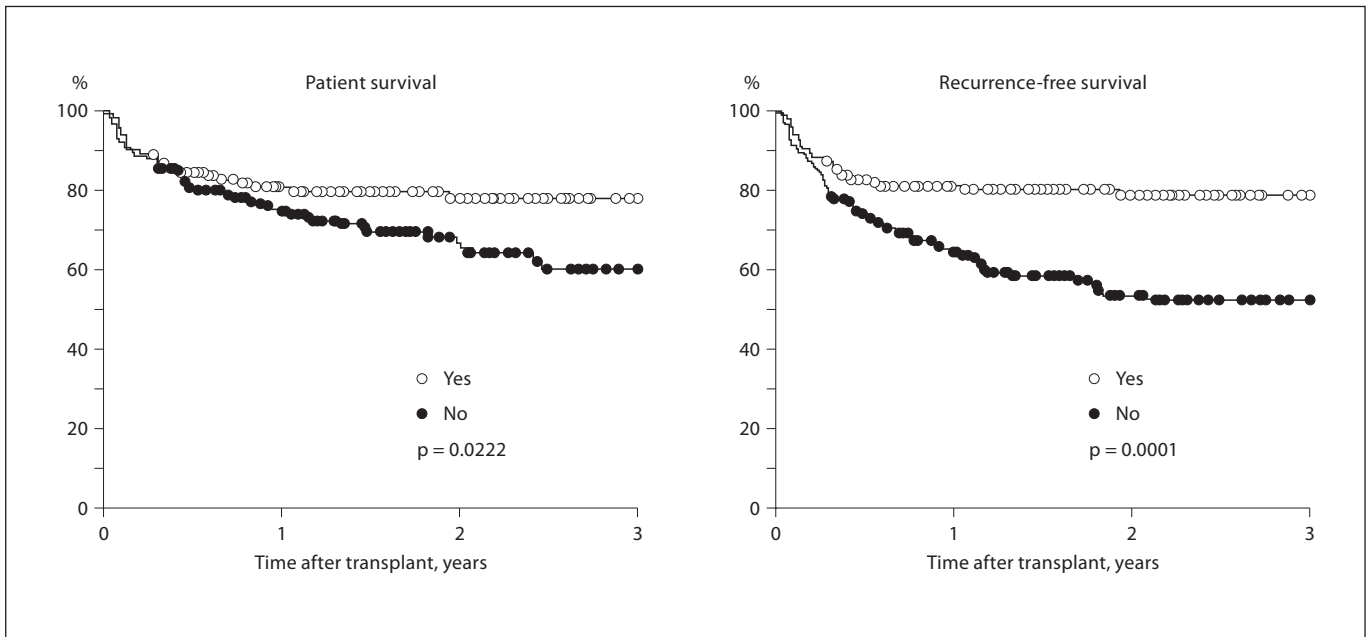


Fig. 1. Patient and recurrence-free survival in relation to the Milan criteria. From Todo et al. [8].

ters in Japan. Among these cases, 3,218 (99.1%) were LDLTs. The 5-year survival rates of grafts from cadaveric and living donors were 80.4 and 75.0%, respectively. LDLT for neoplastic diseases was performed in 520 cases (16.6%), of which 479 (92.1%) were HCCs. Other neoplastic diseases included hepatoblastoma (18 cases), metastatic liver disease (10 cases), hemangioma (7 cases), and others (6 cases). The overall 5-year survival rate was 65.7%, which was not significantly different from that of patients who underwent LT for other primary diseases.

LDLT is usually performed between family members and there have always been concerns about whether the Milan criteria can be an accurate indicator for LDLT. From January 2004, LT for end-stage liver disease in adults was approved by the government-based health insurance system in Japan, and patients with HCC associated with end-stage liver disease were considered eligible for LT covered by the health insurance system only if they met the Milan criteria. In the current system, whether patients fulfill the Milan criteria is judged by postoperative pathologic evaluation. Basically, if this reveals that a recipient with HCC does not fulfill the Milan criteria, then the patient and the transplant center are not reimbursed with the total cost of LDLT. This particular environment is a significant obstacle to extending the Milan criteria in Japan.

Extending the Milan Criteria

Because the Milan criteria limit the use of LT only to patients at a relatively early stage of HCC, many patients are denied the chance of LT even at the time of diagnosis. Currently, efforts are being made to perform LT for HCC patients who exceed the Milan criteria. At the World Transplant Congress held in Boston in 2006, there were 16 reports of studies that had tried to expand the indications of LT beyond the Milan criteria. There are two major options for expanding the criteria, one of which is simply to perform LT for patients who would normally be excluded. Tamura et al. [10] reported that they performed LDLT for patients with up to 5 HCC nodules with a maximum diameter of 5 cm (the so-called '5-5 rule'). The 3-year recurrence-free survival rates in patients who satisfied and did not satisfy the 5-5-rule were 94 and 50%, respectively [10]. The rate for patients who satisfied the rule was comparable to that of patients who fulfilled the Milan criteria. Gondolesi et al. [11] performed LT for 12 patients with HCCs larger than 5 cm in diameter, and used adjuvant chemotherapy consisting of doxorubicin. The 2-year survival and recurrence-free survival rates were 60 and 74%, respectively, which were not different from those of patients whose tumors were less than 5 cm in diameter [11]. These two studies were limited by the

small number of cases and the short-term observation period.

The other way to perform LT for patients who do not fulfill the Milan criteria is to down-stage HCC preoperatively by locoregional therapy. However, the use of locoregional therapies, such as transarterial chemoembolization (TACE) and radiofrequency ablation, before LT is still controversial. Gadano et al. [12] performed TACE in 77 patients with unresectable HCC, and 13 patients responded to such a degree that they fulfilled the Milan criteria. The recurrence-free survival rate of these patients at a mean follow-up point of 38.7 months was 61.5%, which was significantly lower than that of patients who satisfied the Milan criteria at initial presentation (87.5%) [12]. Otto et al. [13] performed TACE in HCC patients who exceeded the Milan criteria prior to LT. Patients who responded to TACE, with a 30% decrease in the sum of the largest diameter of tumor nodules, showed a 5-year recurrence-free survival rate of 74.5%, which was not significantly different from that of patients who did fulfill the Milan criteria. The recurrence-free survival rate for patients who showed no or a minimal response to TACE was significantly lower (35.4 %) [13]. Thus TACE might be useful not only for down-staging HCC but also for evaluating the biological criteria of HCC in relation to LT [14].

Chen et al. [15] reported the clinical results of radiofrequency ablation for patients with HCCs. They successfully ablated HCCs in 90–95% of cases, the local recurrence rate was 5–10%, and the 3-year survival rate was 62–68%. Because these outcomes were not different from that of LT, pretransplant tumor ablation will be a promising tool for down-staging HCCs.

Infections

According to the report by the Japanese Liver Transplant Society (JLTS) in 2005 [9], the 480 patients who underwent LTs included 160 with HBV- and 277 with HCV-associated chronic hepatopathy. Control of HBV and HCV is a crucial issue for successful LT.

For patients with HBV, the recent induction of antiviral prophylaxis, lamivudine, and HBV immunoglobulin (HBIg) has significantly improved the outcome of LT. Prevention of graft re-infection can be achieved by injection of high-dose HBIg during the anhepatic phase, with repeated injections during the early postoperative period. However, prophylaxis with HBIg is not effective for patients who are HBeAg-positive at the time of transplanta-

tion. In these patients, serum HBsAg reportedly became positive in the first 6 months and was sustained. Lamivudine provides effective prophylaxis for HBIg; it can lower the serum HB titer before LT, and continuous intake can maintain viral inhibition after LT. Patients with lamivudine-resistant HBV are currently treated with adenovir [16] and tenofovir [17].

Prevention of recurrent HCV hepatitis after LT is more difficult than prevention of HBV hepatitis. Most recipients who are HCV-positive preoperatively suffer recurrence of HCV hepatitis after LT, and such a recurrence is more frequent in LDLT than in cadaveric LT [18]. Although treatment for recurrent HCV hepatitis using pegylated interferon and ribavirin is effective, tolerance to the regimen is very poor because of the side effects, such as fatigue and pancytopenia [19]. The JLTS report indicated that the graft survival rate was similar between recipients with and without HCV infection, and that HCV genotype 1a may be a risk factor for graft loss [20]. Prevention of recurrent HCV hepatitis after LT remains an important issue.

Immunosuppression

Most Japanese liver transplant centers use a conventional immunosuppressive regimen for HCC patients undergoing LT, consisting of steroid, cyclosporine or tacrolimus, and mycophenol mofetil. Because rapamycin (sirolimus), a mTOR inhibitor, has not only an immunosuppressive but also an antineoplastic effect, an immunosuppressive regimen containing rapamycin is a rational regimen for patients undergoing LT for HCC. Furthermore, Toso et al. [21] have reported that a regimen including rapamycin improved the 4-year recurrence-free survival rate in patients who exceeded the Milan criteria (66.8%).

Currently, rapamycin is not available in Japan and most Japanese liver transplant centers do not use an immunosuppressive regimen specific for HCC. Therefore it is expected that a rapamycin regimen will be tested in Japan in the coming decade.

Concluding Remarks

The liver is the only organ for which primary carcinoma is a major indication for organ transplantation. The shortage of donor livers has limited the allocation of grafts to recipients who do not fulfill the Milan criteria.

LDLT is usually a gift of life from blood relatives or family members to affected patients. Fathers, mothers, brothers, sisters, husbands, and wives may wish to donate part of their liver to a loved one, and LDLT is not restricted by the organ transplantation law in Japan. Thus, it is antici-

pated that the environment of LDLT will provide a breakthrough for performing LT over the limitation of Milan criteria. It will be likely to start LT using new indication for LT for HCC in Japan where most LT are performed between blood connections.

References

- Starzl TE, Putnam CW: Experience in Hepatic Transplantation. Philadelphia, Saunders, 1969.
- Iwatsuki S, Klintmalm GBG, Starzl TE: Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. *World J Surg* 1982;6:81-85.
- Penn I: Hepatic transplantation for primary and metastasis cancers of the liver. *Surgery* 1991;110:726-735.
- Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L: Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-699.
- Zavaglia C, De Carlis L, Alberti AB, Minola E, Belli LS, Slim AO, Airolidi A, Giacomoni A, Rondinara G, Tinelli C, Forti D, Pinzello G: Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. *Am J Gastroenterol* 2005;100:2708-2716.
- Llovet JM, Fuster J, Bruix J: Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30:1434-1439.
- <http://www.unos.org/resources/MeldPeld-Calculator.asp?index=98>.
- Todo S, Furukawa H; on behalf of the Japanese Study Group on Organ Transplantation: Living donor liver transplantation for adult patients with hepatocellular carcinoma. Experience in Japan. *Ann Surg* 2004;240:451-461.
- [http://jlt.umin.ac.jp/Registry\(2005\).pdf](http://jlt.umin.ac.jp/Registry(2005).pdf).
- Tamura S, Sugawara Y, Kaneko J, Kishi Y, Akamatsu N, Yamashiki N, Kokudo N, Makuuchi M: Live donor liver transplantation for hepatocellular carcinoma (abstract 832). *Am J Transplant* 2006;6(suppl 2):348.
- Gondolesi GE, Roayadie S, Muñoz L, Kim-Schuger L, Schiano T, Fishbein TM, Emre S, Miller CM, Schwartz ME: Adult living donor liver transplantation for patients with hepatocellular carcinoma. Extending UNOS priority criteria. *Ann Surg* 2004;239:142-149.
- Gadano A, Galdame O, Monaco RG, Villamil A, Bandi JC, Casciato P, Mullen E, Gallo G, Ardiles V, Pekolj J, Matterna J, Ciardullo M, de Santibanes E: Rescue of patients with unresectable hepatocellular carcinoma with pre-transplant transarterial chemoembolization is associated with increased post-transplant recurrence (abstract 2787). *Am J Transplant* 2006;6(suppl 2):974.
- Otto G, Herber S, Heise M, Lohse AW, Monch C, Bittinger F, Hoppe-Lotichius M, Schuchmann M, Victor A, Pitton M: Response to transarterial chemoembolization as a biological selection criterion for liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2006;12:1260-1267.
- Otto G, Heise M, Moench C, Herber S, Bittinger F, Schuchmann M, Pitton M: Liver transplantation for hepatocellular carcinoma: response to transarterial chemoembolization as a biological selection criterion (abstract 2776). *Am J Transplant* 2006;6(suppl 2):970.
- Chen, MShan, Jin-Qing LMD, Yun Z, Rong-Ping G, Hui-Hong L, Ya-Qi Z, Xiao-Jun L, Wan YL: A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006;243:321-328.
- Perrillo R, Hann HW, Mutimer D, Willems B, Leung N, Lee WM, Moorat A, Gardner S, Woessner M, Bourne E, Brosgart CL, Schiff E: Adenovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004;126:343-347.
- Neff GW, Nery J, Lau DT, O'Brien CB, Duncan R, Shire NJ, Ruiz P, Nery C, Montalbano M, Muslu H, Safdar K, Schiff ER, Tzakis AG, Madariaga JR: Tenofovir therapy for lamivudine resistance following liver transplantation. *Ann Pharmacother* 2004;38:1999-2004.
- Garcia-Retortillo M, Forns X, Llovet JM, Navasa M, Feliu A, Massaguier A, Bruguera M, Fuster J, Garcia-Valdecasas JC, Rimola A: Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. *Hepatology* 2004;40:699-707.
- Verna EC, Gaglio PJ, Dove LM, Kinkhabwala M, Emond JC, Brow RS: Efficacy and safety of prolonged interferon and ribavirin for recurrent hepatitis C following orthotopic liver transplantation (abstract 1408). *Am J Transplant* 2006;6(suppl 2):540.
- Yagci G, Fernandez LA, Knechtle SJ, D'Alessandro AM, Chin LT, Musat AI, Lucey MR, Said A, Pirsch JD, Kalayoglu M: Long-term outcome of liver transplantation for hepatitis C: factors predicting graft loss and mortality (abstract 1406). *Am J Transplant* 2006;6(suppl 2):539.
- Toso C, Meeberg GA, Bigam DL, Ma MM, Wong WWS, Mason AL, Oberholzer J, Shapiro JAM: De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcome and side-effects (abstract 1939). *Am J Transplant* 2006;6(suppl 2):712.

Status of Surgical Treatment of Biliary Tract Cancer

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Key Words

Biliary tract carcinoma · Bile duct carcinoma, hilar, middle, distal · Gallbladder carcinoma · Papilla of Vater carcinoma · Biliary surgery, 5-year survival · Disease stage

Abstract

Complete surgical resection of biliary tract carcinoma remains the best treatment. The Japanese Society of Biliary Surgery has organized a registry project and established a classification of biliary tract carcinoma. We report here the status of biliary surgery in Japan. For hilar bile duct carcinoma, major hepatectomy is needed to increase the resection rate, and total caudate lobectomy is required for curative resection. The 5-year survival rate was 39.1%. Middle and distal bile duct carcinomas were treated with pancreatoduodenectomy (PD) or pylorus-preserving PD (PPPD) or bile duct resection alone. The 5-year survival rate was 44.0%. The treatment of gallbladder carcinoma with pT1 lesions is cholecystectomy. The treatment of pT2 lesions is extended cholecystectomy or various hepatectomy with or without extrahepatic bile duct resection along with lymphadenectomy. Treatment of pT3 and pT4 lesions includes hepatectomy with or without bile duct resection, combined with vascular re-

section, extended lymphadenectomy, and autonomic nerve dissection. Several groups in Japan have performed hepato-pancreatoduodenectomy. The 5-year survival rate of pT1, pT2, pT3, and pT4 were 93.7, 65.1, 27.3, and 13.8%. PD or PPPD is the standard operation for carcinoma of the papilla of Vater. The 5-year survival rate was 57.5%.

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Introduction

Complete surgical resection of biliary tract carcinoma remains the best treatment for long-term survival. In Japan, the Japanese Society of Biliary Surgery (JSBS) is organized into 225 institutions. It performs registration of biliary tract carcinomas as one of its projects. In this project, the society has established guidelines for the treatment of cancer of the biliary tract based on the extent of involvement at each site. A total of 3,518 cases of biliary tract carcinoma were registered between 1998 and 2002; the site of carcinoma was the bile duct in 1,669, the gallbladder in 1,345, and the papilla of Vater in 504 cases. These cases were analyzed with regard to patient survival. We report the status of biliary surgery in Japan.

Classification of Biliary Tract Carcinoma

As noted above, the JSBS established guidelines for the treatment of cancer of the biliary tract based on the extent of involvement at each site, according to the Classification of Biliary Tract Carcinoma currently used in Japan, and the 2nd English edition was published in 2004 [1]. The guidelines promoted in Japan for the treatment of biliary tract carcinoma are divided into three anatomical regions: the biliary duct, gallbladder, and papilla of Vater.

Bile Duct Carcinoma

Staging

Extrahepatic carcinomas have been subdivided into proximal or hilar, middle, and distal subgroups. The histological extent of tumor invasion around the bile duct (t category) in the classification of biliary tract carcinoma of JSBS is defined as the degree of tumor extension. According to the currently used Japanese classification of tumor invasion into the bile duct wall, serosal invasion is histologically divided into 5 stages, m, fm, ss, se, and si, in anatomical fashion. Furthermore, various types of direct invasion of the carcinoma into four structures present around the bile duct, i.e., invasion of the hepatic parenchyma (hinf), pancreatic parenchyma (panc), portal venous system (p), and arterial system (a), are graded from 0 to 3. Nodal involvement of carcinoma is classified into four groups. The stages of biliary tract carcinoma of JSBS are classified into five groups [1].

Hilar Bile Duct Carcinoma

Long-term survival with hilar bile duct carcinoma depends critically on complete resection with negative margins. The resection rate increases with the performance of major hepatectomy, and the likelihood of negative margins by performing it rises in hilar bile duct carcinoma. In addition, total caudate lobectomy is required for curative resection since caudate branches join the hilar bile duct [2, 3]. However, the risk of developing hepatic failure as a postoperative complication increases when major hepatectomy is performed. Therefore, when major hepatectomy is planned, portal vein embolization (PVE) is performed in many Japanese institutions. The main purpose of PVE is to induce compensatory hypertrophy of the future remnant liver and thus minimize postoperative liver dysfunction. In the recent literature from high-volume centers in Japan [4–11], the mortality

Table 1. Surgical procedure for hilar bile duct carcinoma

| Type of hepatectomy | Cases | With PD | With PV | With HA |
|----------------------------|-------|---------|---------|---------|
| Left hepatectomy | 54 | 2 | 2 | 1 |
| Extended left hepatectomy | 66 | 9 | 6 | 3 |
| Left trisegmentectomy | 10 | 1 | 2 | |
| Right hepatectomy | 35 | 8 | 1 | |
| Extended right hepatectomy | 69 | 9 | 4 | |
| Right trisegmentectomy | 18 | 4 | 2 | |
| Central bisegmentectomy | 3 | | | |
| Total | 255 | 29 | 17 | 8 |

PD = Pancreatoduodenectomy; PV = resection and construction of the portal vein; HA = resection and construction of the hepatic artery.

rate ranged from 0 to 12%. The overall 3- and 5-year survival rates ranged from 26 to 54.8% and 23 to 40%, respectively. The proportion of stage IVa (5th edition of UICC) or over stage III (6th edition of UICC) ranged from 41 to 72%. A total of 255 cases of hilar bile duct carcinoma subjected to major hepatectomy were registered in the JSBS between 1998 and 2002 (table 1). The surgical procedure was left hepatectomy in 54 patients, extended left hepatectomy in 66 patients, left trisegmentectomy in 10 patients, right hepatectomy in 35 patients, extended right hepatectomy in 69 patients, right trisegmentectomy in 18 patients, and central bisegmentectomy in 3 patients. Bloc hepatic resection with pancreatoduodenectomy (HPD) was performed in 29 patients. Portal vein resection and reconstruction was performed in 167 patients. Resection of the right or left hepatic artery and reconstruction was performed in 78 patients. The overall the 1-, 2-, 3-, and 5-year survival rates of patients who underwent major hepatectomy were 77.3, 55.9, 46.7, and 39.1%, respectively. Patients were grouped according to the Japanese classification as stage I (n = 21, 8.2%), stage II (n = 45, 17.6%), stage III (n = 66, 25.9%), stage IVa (n = 86, 33.7%), or stage IVb (n = 37, 14.5%). The 5-year survival rate was 90.0% in stage I patients, 57.7% in stage II, 46.2% in stage III, 29.9% in stage IVa, and 17.0% in stage IVb patients (fig. 1). Compared with high-volume centers in Japan, the overall survival rate of the JSBS is good. This difference in survival rate is attributable to the higher percentage of cases of advanced cancer among those undergoing surgery at high-volume centers in Japan where aggressive surgery is often performed for advanced cancer.

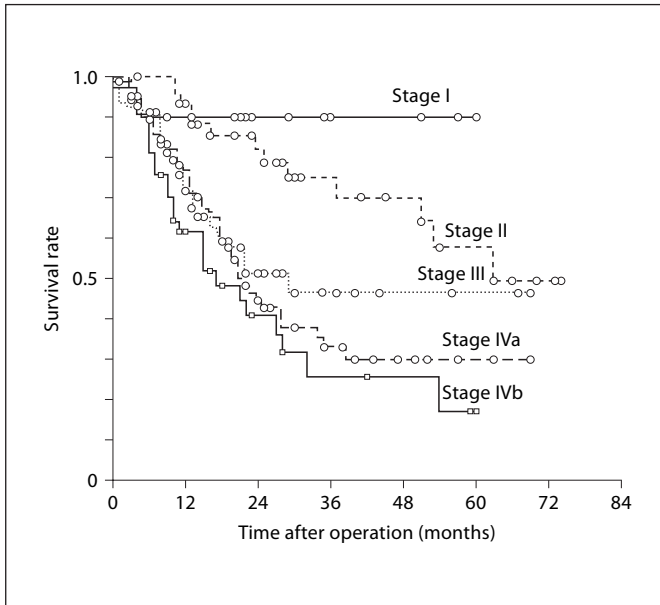


Fig. 1. Survival rates of hilar bile duct carcinoma according to stage.

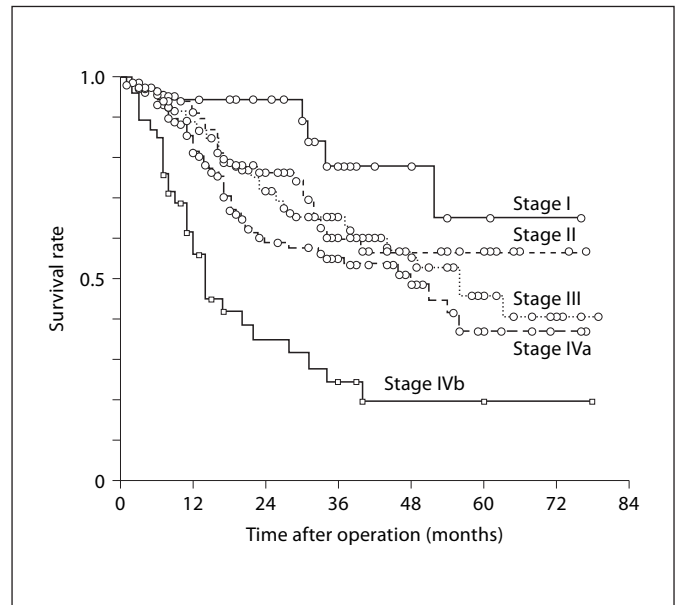


Fig. 2. Survival rates of middle and distal bile duct carcinoma according to stage.

Table 2. Studies of middle and distal bile duct carcinoma

| Reference | Year | Location of tumor | Patients | 3-Year survival, % | 5-Year survival, % |
|-----------------------|------|-------------------|----------|--------------------|--------------------|
| Yamaguchi et al. [12] | 1997 | Distal | 11 | 38 | 19 |
| Yamaguchi et al. [12] | 1997 | Middle | 11 | 33 | 11 |
| Kayahara et al. [13] | 1999 | Middle and distal | 50 | 47 | 35 |
| Suzuki et al. [14] | 2000 | Middle and distal | 99 | 50 | 37.4 |
| Sasaki et al. [15] | 2001 | Middle and distal | 59 | 42.6 | 33.6 |
| Yoshida et al. [16] | 2002 | Distal | 27 | 37 | 37 |
| Sakamoto et al. [17] | 2005 | Middle and distal | 55 | 52 | 24 |

Middle and Distal Bile Duct Carcinoma

Middle and distal bile duct carcinoma is treated with pancreatoduodenectomy (PD) or pylorus-preserving PD (PPPD) or bile duct resection alone. In Japan, some surgeons have advocated complete removal of the primary bile duct cancer with connective tissue clearance, including lymph nodes and neural plexus dissection. Recent results reported from high-volume centers in Japan are summarized (table 2) [12–17]. The overall 3- and 5-year survival rates ranged from 33 to 52% and 11 to 37.4%, respectively. 427 patients with middle and duct carcinoma, excluding those with insufficient data, who underwent PD or PPPD were registered in the JSBS between 1998 and 2002. The overall 1-, 2-, 3-, and 5-year survival rates were 83.5, 66.6, 57.9, and 44.0%, respectively. Patients were

grouped according to the Japanese classification as stage I (n = 36, 8.4%), stage II (n = 82, 19.2%), stage III (n = 134, 31.4%), stage IVa (n = 130, 30.4%), or stage IVb (n = 45, 10.5%). The 5-year survival rates were 64.8% in stage I patients, 56.9% in stage II, 45.6% in stage III, 36.8% in stage IVa, and 19.5% in stage IVb (fig. 2).

Gallbladder Carcinoma

Staging

The histological extent of tumor invasion around the gallbladder (t category) in the classification of gallbladder carcinoma of the JSBS is defined as the degree of tumor extension. According to the currently employed Japanese

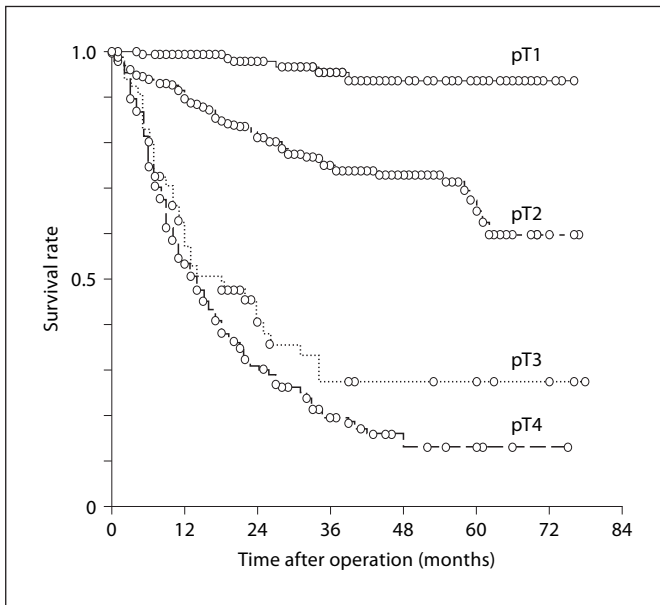


Fig. 3. Survival rates of gallbladder carcinoma according to depth of invasion.

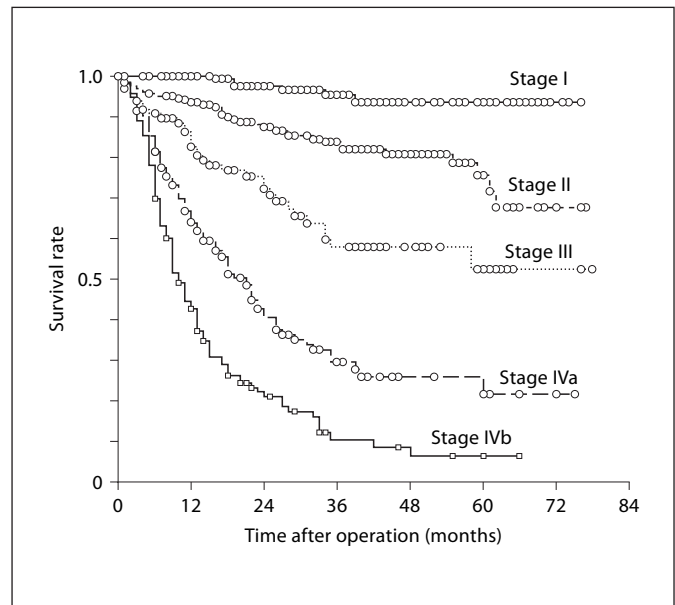


Fig. 4. Survival rates of gallbladder carcinoma according to stage.

classification of tumor invasion into the bile duct wall, serosal invasion is histologically classified into five stages, m, mp, ss, se, and si, in accordance with the anatomical structure. Furthermore, various types of direct invasion of carcinoma into four structures present around the bile duct are distinguished, i.e., invasion of the hepatic parenchyma (hinf), hepatoduodenal ligament (binf), portal venous system (p), and arterial system (a), which are graded from 0 to 3. Nodal involvement of gallbladder carcinoma is classified into four groups. The stages of biliary tract carcinoma of the JSBS are classified into five groups [1].

Surgery

Most surgeons agree that pT1 tumors are effectively treated with cholecystectomy. The 1-, 2-, 3-, and 5-year survival rates of pT1 patients (n = 160) registered with the JSBS were 99.4, 97.8, 95.4, and 93.7%, respectively (fig. 3). pT2 tumors often exhibit lymph node metastases. 30% (93/306) of the T2 tumors registered with JSBS were associated with lymph node metastases. Lymph node dissection is thus necessary for pT2 gallbladder carcinoma. Extended cholecystectomy or various types of hepatectomy with or without extrahepatic bile duct resection have been performed for pT2 patients in Japan. The range of liver resection required as part of radical surgery is still controversial. The 1-, 2-, 3-, and 5-year survival rates of

T2 patients (n = 306) registered with the JSBS were 89.8, 81.1, 75.2, and 65.1%, respectively (fig. 3). For pT3 and pT4 tumors, the surgical procedures currently used in Japan include various types of hepatectomy with or without bile duct resection, combined vascular resection, extended lymphadenectomy, and autonomic nerve dissection. Several surgical groups in Japan have performed HPD for locally advanced gallbladder carcinoma. The usefulness of extrahepatic bile duct resection as part of radical surgery for advanced gallbladder carcinoma is also still controversial, particularly when there is no apparent extrahepatic bile duct involvement. The 1-, 2-, 3-, and 5-year survival rates of pT3 patients (n = 66) registered with the JSBS were 57.7, 41.0, 27.3, and 27.3%, while those for pT4 patients (n = 228) were 53.6, 30.3, 19.5, and 13.8%, respectively (fig. 3).

760 patients with gallbladder carcinoma, excluding those with insufficient data, who underwent resection were registered in the JSBS between 1998 and 2002. The overall 1-, 2-, 3-, and 5-year survival rates were 78.2, 66.3, 58.9, and 52.6%, respectively. There are two papers concerning large numbers in Japan from different periods. The 5-year survival rate of 1,686 patients with resection between 1979 and 1988 was 30.1% [18], while that of 3,249 patients with resection between 1988 and 1998 (JSBS) was 42% [19]. Patients were grouped according to the Japanese classification as stage I (n = 160, 8.4%), stage II

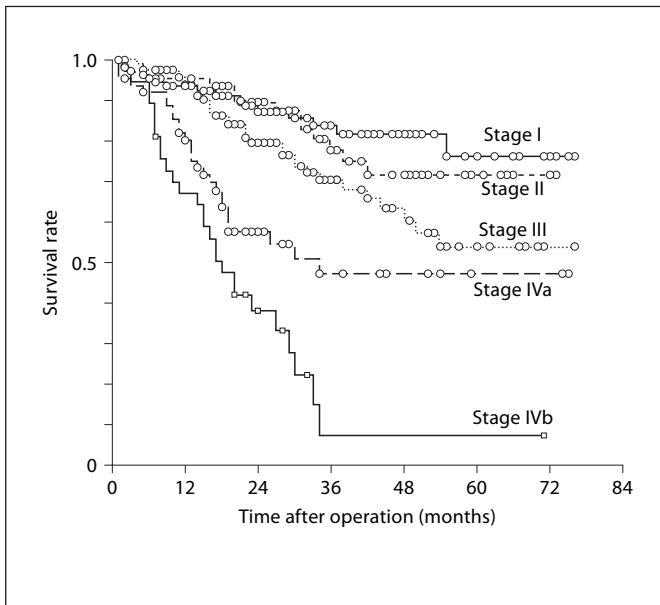


Fig. 5. Survival rates of carcinoma of the papilla of Vater according to stage.

Table 3. Studies of carcinoma of the papilla of Vater

| Reference | Year | Patients | 3-Year survival, % | 5-Year survival, % |
|----------------------|------|----------|--------------------|--------------------|
| Kawarada et al. [20] | 1993 | 89 | 63.6 | 57.4 |
| Nakao et al. [21] | 1994 | 26 | 57.7 | 52.3 |
| Shirai et al. [22] | 1996 | 35 | 60 | |
| Kayahara et al. [23] | 1997 | 36 | 66 | 56 |
| Tanaka et al. [24] | 2002 | 16 | 58.9 | 55 |

(n = 208, 19.2%), stage III (n = 98, 31.4%), stage IVa (n = 152, 30.4%), or stage IVb (n = 142, 10.5%). The 5-year survival rate was 93.6% in stage I patients, 80.8% in stage II, 52.6% in stage III, 21.5% in stage IVa, and 6.5% in stage IVb (fig. 4).

Carcinoma of the Papilla of Vater

Staging

The histological extent of tumor invasion around the papilla of Vater (t category) in the classification of gallbladder carcinoma of the JSBS is defined as the degree of tumor extension. Various types of histologically direct invasion of the carcinoma into two structures present

around the papilla of Vater, i.e. the pancreatic parenchyma (panc) and duodenum (du), are graded from 0 to 3. Nodal involvement of gallbladder carcinoma is classified into four groups. The stages of biliary tract carcinoma of JSBS are classified into five groups [1].

Surgery

In most series, the resectability rate is higher than for other malignant tumors of the periampullary region. PD or PPPD is the standard operation for carcinoma of the papilla of Vater. Recent reports from high-volume centers in Japan are summarized (table 3) [20–24]. The overall 3- and 5-year survival rates ranged from 55 to 66% and from 40 to 60%, respectively. 404 patients with carcinoma of papilla of Vater, excluding those with insufficient data, who underwent PD or PPPD were registered in the JSBS between 1998 and 2002. The overall 1-, 2-, 3-, and 5-year survival rates were 89.3, 75.6, 66.0, and 57.5%, respectively. Patients were grouped according to the Japanese classification as stage I (n = 112, 27.7%), stage II (n = 65, 16.1%), stage III (n = 126, 31.2%), stage IVa (n = 64, 15.8%), or stage IVb (n = 37, 9.2%). The 5-year survival rates were 76.3% in stage I patients, 71.7% in stage II, 54.0% in stage III, 47.2% in stage IVa, and 7.4% in stage IVb (fig. 5).

Conclusion

We report the status of biliary surgery in Japan. Hilar bile duct carcinoma is one of the diseases on which Japanese biliary tract surgeons place particular emphasis. PVE performed during major hepatectomy and total caudate lobectomy have contributed to improving the outcome of treatment of hilar bile duct carcinoma. Middle and distal bile duct carcinomas are treated with PD or PPPD or bile duct resection alone. The treatment of gallbladder carcinoma with pT1 lesions is cholecystectomy. The treatment of pT2 lesions is extended cholecystectomy or various hepatectomy with or without extrahepatic bile duct resection, and lymphadenectomy. The treatment of pT3 and pT4 lesions includes various types of hepatectomy with or without bile duct resection combined vascular resection, extended lymphadenectomy, and autonomic nerve dissection. The usefulness of resection of the extrahepatic bile duct and the range of liver resection of gallbladder carcinoma are still controversial. Several groups in Japan perform HPD for locally advanced gallbladder carcinoma. PD or PPPD is the standard operation for carcinoma of the papilla of Vater.

References

- 1 Japanese Society of Biliary Surgery: Classification of Biliary Tract Carcinoma, second English edition. Tokyo, Kanehara, 2004.
- 2 Mizumoto R, Suzuki H: Surgical anatomy of hepatic hilum with special reference to the caudate lobe. *World J Surg* 1988;12:2–10.
- 3 Nimura Y, Hayakawa N, Kamiya J, et al: Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. *World J Surg* 1990;14:535–544.
- 4 Miyazaki M, Ito H, Nakagawa K, et al: Parenchyma-preserving hepatectomy in surgical treatment of hilar cholangiocarcinoma. *J Am Coll Surg* 1999;189:575–583.
- 5 Kosuge T, Yamamoto J, Shimada K, et al: Improved surgery results for hilar cholangiocarcinoma. *Ann Surg* 1999;230:663–671.
- 6 Todoroki T, Kawamoto T, Koike N, et al: Radical resection of hilar bile duct carcinoma and predictors of survival. *Br J Surg* 2000;87:306–313.
- 7 Tabata M, Kawarada Y, Yokoi H, et al: Surgical treatment for hilar cholangiocarcinoma. *J Hepatobiliary Pancreat Surg* 2000;7:148–154.
- 8 Seyama Y, Kubota K, Sano K, et al: Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. *Ann Surg* 2003;238:73–83.
- 9 Kawasaki S, Imamura H, Kobayashi A, et al: Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. *Ann Surg* 2003;238:84–92.
- 10 Kondo S, Hirano S, Ambo Y, et al: Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study. *Ann Surg* 2004;240:95–101.
- 11 Nagino S, Kamiya J, Nishio H, et al: Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg* 2006;243:364–372.
- 12 Yamaguchi K, Chijiwa K, Saiki S, et al: Carcinoma of extrahepatic bile duct: mode of spread and its prognostic implications. *Hepatogastroenterology* 1997;44:1256–1261.
- 13 Kayahara M, Nagakawa T, Ohta T, et al: Role of nodal involvement and the periductal soft-tissue margin in middle and distal bile duct cancer. *Ann Surg* 1999;229:76–83.
- 14 Suzuki M, Unno M, Oikawa M, et al: Surgical treatment and postoperative outcomes for middle and lower bile duct carcinoma in Japan—experience of a single institute. *Hepatogastroenterology* 2000;47:650–657.
- 15 Sasaki R, Takahashi M, Funato O, et al: Prognostic significance of lymph node involvement in middle and distal bile duct cancer. *Surgery* 2001;129:677–683.
- 16 Yoshida T, Matsumoto T, Sasaki A, et al: Prognostic factors after pancreatoduodenectomy with extended lymphadenectomy for distal bile duct cancer. *Arch Surg* 2002;137:69–73.
- 17 Sakamoto Y, Kosuge T, Shimada K, et al: Prognostic factors of surgical resection in middle and distal bile duct cancer: an analysis of 55 patients concerning the significance of ductal and radical margins. *Surgery* 2005;137:396–402.
- 18 Ogura Y, Mizumoto R, Isaji S, et al: Radical options for carcinoma of gallbladder: present status in Japan. *World J Surg* 1991;15:337–343.
- 19 Nagakawa T, Kayahara M, Ikeda S, et al: Biliary tract cancer treatment: results from the biliary tract cancer statistics registry in Japan. *J Hepatobiliary Pancreat Surg* 2002;9:569–575.
- 20 Kawarada Y, Takahashi K, Tabata M, et al: Surgical treatment for carcinoma of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 1993;1:8–13.
- 21 Nakao A, Harada A, Nonami T, et al: Prognosis of cancer of the duodenal papilla of Vater in relation to clinicopathological tumor extension. *Hepatogastroenterology* 1994;41:650–657.
- 22 Shirai Y, Tsukada K, Ohtani T, et al: Carcinoma of the ampulla of Vater: is radical lymphadenectomy beneficial to patients with nodal disease? *J Surg Oncol* 1996;61:190–194.
- 23 Kayahara M, Nagakawa T, Ohta T, et al: Surgical strategy for carcinoma of the papilla of Vater on basis of lymphatic spread and mode recurrence. *Surgery* 1997;121:611–617.
- 24 Tanaka S, Hirohashi K, Tanaka H, et al: Prognostic factors in patient with carcinoma of the papilla of Vater. *Hepatogastroenterology* 2002;49:1116–1119.

Introductory Remarks

Digestive cancer is one of the leading causes of death in the world and appropriate treatment of digestive cancer is a common subject for all gastroenterological surgeons. Digestive cancer itself is not essentially and pathologically different between countries or areas. However, there are differences in prevalence and pathogenesis between countries or areas, even in cases of the pathologically same cancer. The differences are on the basis of social and cultural differences such as environment, foods, customs, and so on. For example, *Helicobacter pylori* infection plays a pivotal role in the development of not only antral cancer but also cardiac cancer in Eastern countries. On the contrary in Western countries, especially in the US, gastroesophageal reflux with hyperacidity plays an important role in cardiac carcinogenesis. Hepatocellular carcinoma in Eastern countries is closely related to viral infection, but to excessive alcohol intake in Western countries. Accordingly, the diagnostic methods, surgical treatment and prevention of digestive cancer are different among countries. In addition, the health service system and socioeconomic reasons may bring about many differences.

Taken together, not only to discuss the essential and common knowledge of digestive cancer, but also to recognize the underlying social and cultural differences between countries or areas is likely to provide new and better approaches to the diagnosis, treatment and preven-

tion of digestive cancer. It is true that there are some differences in diagnostic methods, surgical treatment, chemotherapy and prevention of digestive cancer between Japan and Western countries. Mutual exchange of updated knowledge is a key for advances in basic and clinical research and for much better clinical results. From this viewpoint, this special issue of *Digestive Surgery* was planned and presents the current topics of surgical treatment of digestive cancer in Japan. This special issue will undoubtedly reduce the differences between countries.

Digestive Surgery is the collaborative official journal of the Japanese Society of Gastroenterological Surgery (JSGS). The JSGS consists of 22,000 active members and publishes monthly the *Japanese Journal of Gastroenterological Surgery* in Japanese. The annual congress of JSGS is held in July in which more than 2,500 scientific papers are presented and more than 6,000 members participate. In addition, many papers from the members of JSGS are submitted to *Digestive Surgery* every year.

On behalf of JSGS, I would like to express our deepest appreciation to the authors, the editors and editorial manager of *Digestive Surgery* for publication of this special issue. We are convinced that this special issue will contribute to further advances in the surgical treatment of digestive cancer in the world.

Michio Kaminishi, Tokyo

Current Status of Surgery for Pancreatic Cancer

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Key Words

Pancreatic cancer, incidence · Surgery, pancreatic cancer

Abstract

Background: In Japan the annual incidence of pancreatic cancer has increased over the last decade, but no advancement has been made in the long-term prognosis after resection. The significant differences in the surgical procedures between Western countries and Japan have been discussed. Therefore, an adequate comparison and analysis of the data from Japan, Europe and the USA is required. This review evaluates many important published reports from Japan which influence surgical procedure. **Methods:** Several important highlights and controversies regarding the concept of surgical treatment and surgical procedure are discussed comparing the results in Japan with those in Western countries. **Results:** No significant difference in diagnostic strategy using various imaging methods was observed between Japan and Europe. The stage classification for pancreatic cancer by the Japanese Pancreatic Society (JPS) seems to be superior to others, because the results on long-term prognosis after pancreatectomy of cases with pancreatic head cancer, diagnosed as tubular adenocarcinoma, has been arranged logically. Pancreatectomy with extended radical dissection is recommended in Japan, but several clinical studies from Europe and the USA suggest that this is ineffective. The basic concepts of this controversy have recently come closer altogether. Scientific

clinical trials for instance on the necessity of adjuvant treatment, etc., are now on-going. **Conclusion:** The characteristics on diagnosis and treatment of pancreatic cancer in Japan are described. The JPS registration system for pancreatic cancer can provide much more information, i.e. dependency on diagnostic methods, highly frequent sites of lymph node and of distant metastases, the prognosis of small pancreatic cancers, etc. The indication for any surgical treatments should be limited to cases with the possibility of cancer free margins.

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Introduction

Pancreatic cancer is the fifth leading cause of cancer death in Japan. The lethality of this malignant neoplasm is demonstrated by the annual incidence which is roughly more than 17,000 patients/year. Unfortunately, the incidence of pancreatic cancer is increasing in Japan and, aside from tobacco, its exact risk factors remain poorly understood. Pancreatic cancer registration has been carried out by the Japanese Pancreas Society (JPS) since 1981, and the 5-year survival on this registry after pancreatectomy is 13.1% [1]. According to the JPS classification, the 5-year survival in the cases with stage I, defined as no metastasis to regional lymph nodes and no neural invasion, is 61.0%, and those for stages II, III, IVa and IVb are arranged in a parallel manner. This might suggest the

accuracy of the JPS stage classification and the effectiveness of the surgical procedure for carcinoma of the pancreas. However, the number of the patients with stage I is extremely low (about 1.4%/year) in spite of the development of imaging diagnoses, and most of the cases are still in stage IVa and IVb.

Surgical techniques in Japan have been standardized on a basic treatment concept for invasive pancreatic cancer, which aims for a safe pancreatectomy procedure and aggressive dissection with a negative surgical margin. The results from this concept were expected to show qualitatively better treatment results for advanced pancreatic cancer in Japan during the 1990s. However, a longer survival rate has not yet come about because it is still difficult to diagnose patients with earlier stages of pancreatic cancer even though the screening system should have enabled this. It is well recognized that, upon surgical treatment, pancreatic cancer very often occurs in the retropancreatic extension, has lymph node metastases and neural invasion upon surgical treatment. The Japanese concept in this field recommends extended radical pancreatectomy, but this does not ascertain a better result as opposed to our expectations. A few institutes have had higher 5-year survival results of more than 30% [2–4]. However, these results were not based on a prospective randomized study and include various stages. The similar result on long-term prognosis have been observed in Europe and the USA [5–7], although extreme lymph node dissection and neural plexus dissection have not been performed. The effectiveness of postoperative adjuvant chemotherapy has recently been reported in randomized control trials (RCTs) [8–10]. Also in Japan, several trials on surgical procedures and adjuvant treatment have been reported [11]. In this review, the current status of surgery for pancreatic cancer in Japan is discussed in accordance with the introduction of international and Japanese trends mainly concentrating on the highlights and the controversies.

Diagnosis and Assessment of Resectability

In a patient with confirmed or suspected pancreatic cancer, the first clinical step in management is to determine the resectability and to evaluate of the tumor staging. Most of the clinical features, such as marked and rapid weight loss, persistent back pain, ascites, supraclavicular lymphadenopathy and ascites, are known as risk factors which reflect one or some of distant metastases such as hepatic metastases, systemic lymph node metastases, major stenosis in large vein (portal or superior mes-

enteric vein), neural invasion and peritoneal dissemination. In most cases these pathophysiologies are generally detected by ultrasound sonography, contrast computed tomography (CT), multi-detected CT and MRI. The existence of these features often make a patient select a palliative method such as bypass operation. However, resection of the tumor should be performed whenever no contraindicating risk is found. Pancreatic tumors are considered resectable when CT shows an isolated pancreatic mass without contiguous organ invasion, vascular involvement, nodal metastases, liver metastases or ascites. However, poor preoperative assessment of resectability by CT scan is known in detecting lymph node metastases, scattered local extension and small hepatic metastases. Is helical CT or dynamic MRI better for diagnosis [12]? Following diagnosis of a resectable pancreatic carcinoma, reliable detection of lymph node status is most important with regard to a curable resection. However, it has been reported that the diagnostic accuracy of CT imaging of nodal metastases varies from 42 to 58%, sensitivity 19–37%, specificity 60–92%, positive predictive value 47–83%, and negative predictive value 34–67% [13–16]. According to recent studies on ultrasonographic diagnosis, endoluminal ultrasonography is highly sensitive to detect invasion of major vascular strictures [17, 18]. The effectiveness of endoluminal ultrasonography in the diagnosis of pancreatic cancer gave a sensitivity of 95%, and a specificity of 80%, and negative predictive value of 80% [17]. Kaneko et al. [18] reported similar results with a slightly higher sensitivity of 96.9%, specificity of 91.2% and overall accuracy of 93.9% in the diagnosis of portal invasion. On the other hand, CT analysis resulted in a sensitivity of 83.9%, specificity of 74.3% and overall accuracy of 78.9%. Involvement of the venous system exceeding half the circumference of the vessel on CT is very suggestive of invasion, but this is not so when less than half of the vessel is involved, and it is not adaptable in artery systems. Accordingly, an indicative factor in the diagnosis of local cancer extension has not been established. Direct macroscopic observation and laparoscopic diagnosis are indicated in patients with pancreatic tumors not isolated from the surrounding tissue and vessels.

Importance of Staging

In Japan more than 70% of the pancreatic tumors requiring surgical treatment are located in the head of the pancreas (table 1) [1]. Others are located in the body and/or tail of the pancreas. The possibility of better prognosis

Table 1. Tumor location in the pancreas [1]

| | Location | | | | Total |
|--------------|--------------|--------------|-----------------------------|------------|--------------|
| | head | body-tail | head and body/body and tail | whole | |
| Tumor size | | | | | |
| TS1 (<2 cm) | 638 | 159 | 25 | 2 | 824 |
| TS2 (2–4 cm) | 2,929 | 598 | 240 | 20 | 3,787 |
| TS3 (4–6 cm) | 1,519 | 476 | 479 | 31 | 2,505 |
| TS4 (>6 cm) | 652 | 366 | 773 | 214 | 2,005 |
| Unknown | 346 | 122 | 134 | 54 | 656 |
| Total | 6,084 | 1,721 | 1,651 | 321 | 9,777 |
| Operation | | | | | |
| Resected | 4,913 | 1,254 | 921 | 135 | 7,223 |
| Palliative | 965 | 230 | 517 | 117 | 1,829 |
| Others | 206 | 237 | 213 | 69 | 725 |
| Total | 6,084 | 1,721 | 1,651 | 321 | 9,777 |

by operation is limited to resected cases with Ro operation and no lymph node metastasis. There are several classifications for pancreatic cancer and we would like to compare some representative classifications, i.e. the Japanese Pancreas Society (JPS) classification (table 2a) [1], the 2002 Union International contre la Cancer (UICC) tumor node metastasis (TNM) classification (table 2b) [19], and the American Joint Committee on Cancer (AJCC) (in cooperation with the TNM committee of the International Union Against Cancer) staging system. In their initial versions, there were wide differences in determining the rules on stage-for-stage comparison, but have become much closer together with the latest revisions (table 3). These systems may be contributive as predictive prognostic factors for overall survival, but they are sometimes not useful for planning treatment because patients with advanced stages of disease may not be candidates for surgical resection. This fact has remained the difficulty of staging based on the skill and efforts of surgeons of pancreatic cancer. Otherwise, highly qualified surgeons have given much effort to curability under the rules of the staging systems, but it is very difficult to definitely identify regional metastases and invasion at the macroscopic level in the perioperative period. Most of these cases unfortunately resulted in non-curable operations according to the pathological diagnosis, which contributes to the scientific support of clinical knowledge. Recent improvements in diagnostic systems before/after surgery may contribute somewhat to the prognosis and new treatment, i.e. mo-

lecular target therapy, etc., in near future. Pancreatic cancer is very malign with a high ability to metastasize to the lymph nodes and to invade vessels (lymph canals, arteries and veins) and the perineural region. Therefore, pathological descriptions for these areas should be made.

Much molecular research for the diagnosis of micro-metastases via the lymph system and via the blood stream are of clinical significance; some have proven the significant influence of micrometastases in the resected lymph nodes and/or cancer-positive conditions in the blood stream on survival (table 4) [21–30]. However, diagnostic methods using immunohistochemical or molecular analysis are not supported by medical insurance in Japan. Some molecular research concluded that the relationship between morphological and molecular diagnoses is very useful for prognosis, but each diagnostic value is proven as an independent factor on statistical analysis. In future the development of molecular diagnosis could contribute not only to the strategy for treatment but also to the decision of targeting treatment. At present, no meaningful treatment method, except surgery, has been invented, and a breakthrough, such as the appearance of molecular target drugs, is awaited.

Comparison between JPS and UICC Staging Classifications

Advancements in the treatment of pancreatic cancer in Japan have been supported by the National Pancreatic Cancer Registry of the JPS. The success of this registry has resulted in the provision of macroscopic and microscopic standard criteria, standard guidelines for the diagnosis, treatment, and introduction of risk factors on prognosis. Finally, the JPS classification was established on the basis of these data and it has been recognized that the stage classifications for pancreatic cancer reveal the more stratified and informative criteria. Many Japanese surgeons depend on these staging criteria to determine treatment strategy and obtain informed consent. By analyzing the JPS data on 3,979 patients who underwent resection for tubular adenocarcinoma of the pancreatic head, Isaji et al. [31] recently reported that the JPS classification is more reliable for predicting outcomes as compared with the UICC classification. In the past there have been wide discrepancies in the prognostic results for pancreatic cancer at each stage between Japan and the United States. This might be due to differences in clinical staging between the JPS and the UICC. In 1998, Kawarada et al. [32] compared the JPS 4th edition (1993) and the

Table 2. Stage groupings according to the JPS [1] (a) and UICC [19] (b) classifications

| a JPS | | | | | b UICC | | | | |
|-------|----|-----|-----|----|--------|-----|------|--|----|
| | M0 | | | M1 | | M0 | | | M1 |
| | N0 | N1 | N2 | N3 | N0 | N0 | | | |
| Tis | 0 | | | | | 0 | | | IV |
| T1 | I | II | III | | | IA | | | |
| T2 | II | III | III | | | IB | IIIB | | |
| T3 | II | III | IVa | | | IIA | IIIB | | |
| T4 | IV | | | | | III | III | | |

Wide differences with regard to the grouping are observed for tumor status and lymph node metastasis.

Table 3. Comparison of the definitions for T number in the latest publications between the JPS 5th edition (2002) [1] and the UICC 6th edition (2002) [19]

| Classification | JPS 5th ed. (2002) | UICC 6th ed. (2002) |
|----------------|---|--|
| T1 | Tumor limited to the pancreas, ≤2 cm in greatest dimension | Tumor limited to the pancreas, ≤2 cm in greatest dimension |
| T2 | Tumor limited to the pancreas, >2 cm in greatest dimension | Tumor limited to the pancreas, >2 cm in greatest dimension |
| T3 | Tumor that has extended into any of the following: biliary duct (CH), duodenum (DU), peripancreatic tissue (S, RP) | Tumor extends beyond the pancreas but without involvement of celiac axis or superior mesenteric artery |
| T4 | Tumor that has extended into any of the following: adjacent large vessels (PV, A), extrapancreatic nerve plexus (PL), other organs (OO) | Tumor involves celiac axis or superior mesenteric artery |

Table 4. Detection of disseminated pancreatic cancer cells in the peripheral blood samples from Japanese reports

| Markers | Samples | Positive/total patients (detection rates, %) | References |
|----------------------------|------------------|--|----------------------------|
| K-ras mutation (codon 12) | Peripheral blood | 2/6 (33.3%) | Tada et al. [21], 1993 |
| K-ras mutation (codon 12) | Liver | 13/17 (76.5%) | Inoue et al. [22], 1995 |
| K-ras mutation (codon 12) | Peripheral blood | 10/10 (100%) | Nomoto et al. [23], 1996 |
| K-ras mutation (codon 12) | Lymph nodes | 4/6 (66.6%) | Tamagawa et al. [24], 1997 |
| K-ras mutation (codon 12) | Lymph nodes | 8/13 (61.5%) | Ando et al. [25], 1997 |
| CEA mRNA | Peripheral blood | 3/9 (33.3%) | Funaki [26], 1998 |
| Keratin 19 mRNA (stage IV) | Peripheral blood | 2/19 (10.5%) | Aihara et al. [27], 1997 |
| | Portal blood | 1/18 (5.6%) | |
| CEA mRNA | Peripheral blood | 13/21 (61.9%) | Miyazono et al. [28], 1999 |
| Chymotrypsinogen mRNA | Peripheral blood | 7/10 (70%) | Kuroki et al. [29], 1999 |
| α4GnT mRNA (stage IV) | Peripheral blood | 33/43 (76.7%) | Ishizone et al. [30], 2006 |

UICC 5th edition (1997), and the results showed that the JPS system was more reliable for long-term prognosis. However, the opinion leaders in the Western countries suggested that the rule of classification of the JPS 4th edition was very complicated and not useful clinically. Japa-

nese researchers surely also have a similar impression. Since then, further efforts by the JPS Review Committee of the General Rules on the Study of Pancreatic Cancer have been asked to establish more a simple and reliable staging classification. Finally, the JPS published the 6th

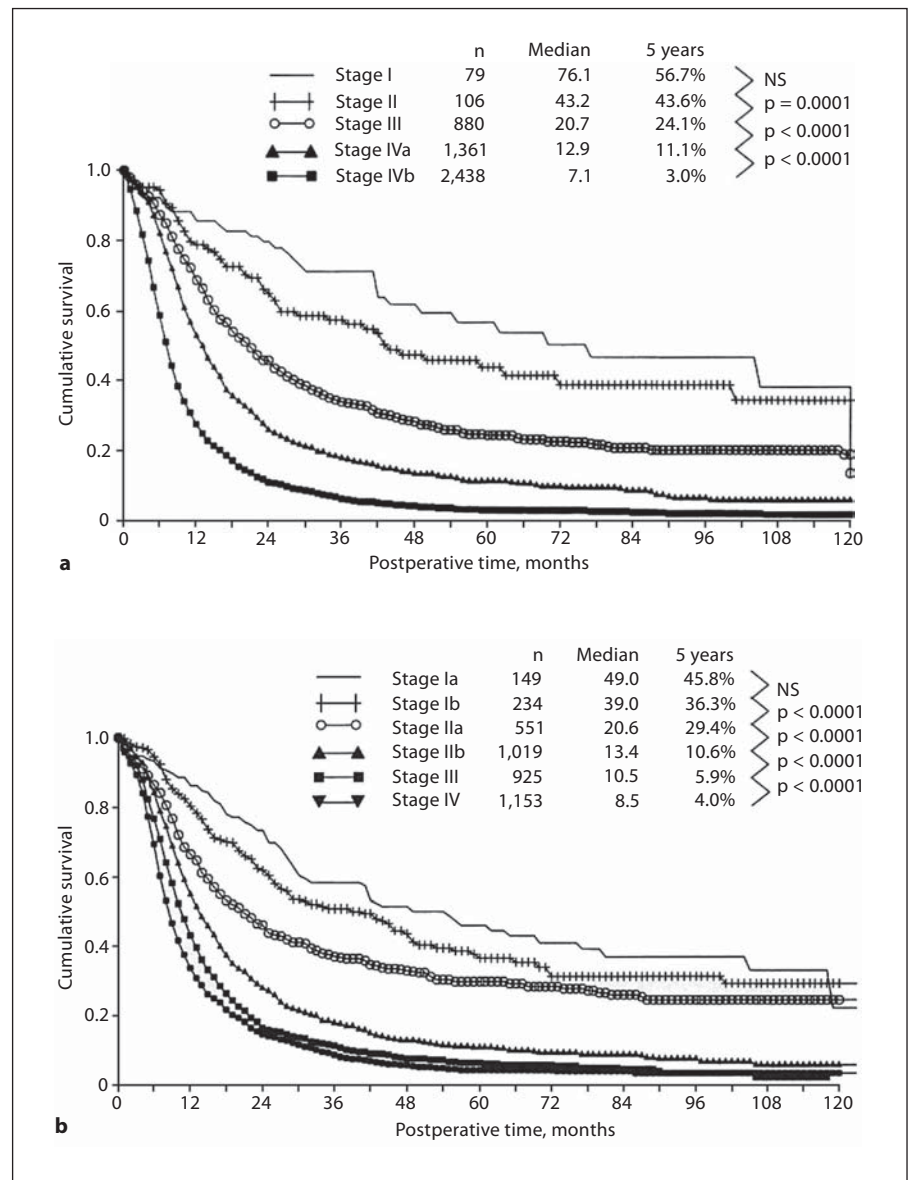


Fig. 1. a Survival curves according to the JPS staging of the patients who underwent resection for tubular adenocarcinoma of the pancreas head. Altogether the survival rates of the five stages differed significantly. **b** Survival curves according to the UICC stages. No difference could be found between stages Ib and IIa, and stages IIb, III and IV [19].

Japanese edition in 2002 and the 2nd English edition in 2003. On the other hand, the 6th edition of UICC was published in 2002, which showed even wider differences in staging from that of the JPS (table 3). Therefore, the first purpose of Isaji et al. [31] was to analyze the results of operative treatment over the last 15 years (18,629 cases) to determine whether the prognosis of pancreatic cancer had improved, and secondly to compare the usefulness of the two classifications on outcome. Generally, it is understood that it is difficult to decide the best research method for such a comparison. Therefore, they focused on the reliability of predicting outcome for 3,979 resected cases with tubular adenocarcinoma localized in the head of

pancreas. The results were as follows: (1) the survival rate was correlated with the Japanese stage classification (fig. 1a); (2) the extent of the primary tumor (T category) indicates the significant difference in the survival rates among the 4 groups in both classifications; (3) the extent of lymph node involvement and of extrahepatic tissue invasion better reflects prognosis by the JPS rules than the UICC rules, and (4) the UICC staging system does not reflect differences in prognosis among the stages, especially between stages Ib and IIa, and stages IIb, III and IV (fig. 1b).

These results indicate that the JPS classification may offer a better prediction of prognosis.

Surgical Treatment

Surgical treatment of pancreatic cancer unfortunately has only a low success rate with regard to its long-term prognosis, and there is only a likelihood of cure following operation [33]. Recent studies in Japan and also in Western countries show that pancreaticoduodenectomy is associated with a 5-year survival of 10–20% [1], which has remained unchanged over the last 10 years. The surgical mortality rate of less than a few percent has improved. The most important prognostic factor for long-term survival after radical resections has been shown to be nodal status. In general, the 5-year survival after pancreaticoduodenectomy is roughly 10% for node-positive disease, while it can be 25–30% for node-negative disease. However, it is impossible to definitely detect the positive lymph nodes before and/or during surgery. Therefore, patients without the contraindications for curative resection, i.e. the presence of distant metastases, peritoneal seeding, tumor infiltration to the celiac artery or superior mesenteric artery extension of tumor tissue into the mesentery, etc., should receive the appropriate radical operation to improve their outcome.

Most hospitals in Japan have experience with extensive radical resection including excision of the portal vein, total or extensive regional pancreatectomy and extensive retroperitoneal lymphadenectomy. Some have suggested the effectiveness of extensive radical resection [2, 3]. However, no evidence from RCTs has been reported.

Current Concept in Japan

In 2004, Matsuno et al. [34] reported the results of 20 years experience with the pancreatic cancer registry in Japan. The total number of cases was 23,302, of which the number of epithelial and non-epithelial tumors were 11,819 and 0, respectively, and the number of the cases without histological diagnosis was 11,483. Data analysis was performed using SPSS software.

The male to female ratio was 1.58:1.00. The overall resectability rate was approximately 40% for the patients who underwent pancreatectomy for invasive cancer in the head of the pancreas. The 5-year survival in the invasive carcinoma group was 9.7%, and wide differences were observed between the various histologies of the resected cases ranging from 10.7 to 44.8% as follows: tubular adenocarcinoma 10.7% (well differentiated type 13.1%, moderately differentiated type 9.3%, poorly differentiated type 9.3%); papillary adenocarcinoma 26.1%; adeno-squamous carcinoma 15.8%, etc. Comparing the 5-year survival limited to cases with tubular adenocarcinoma,

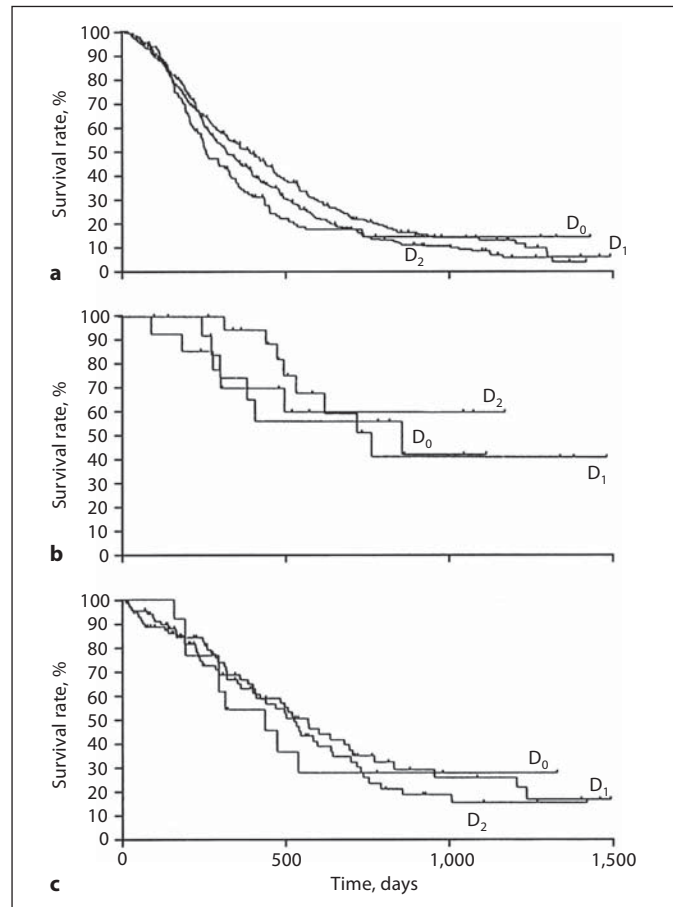


Fig. 2. Cumulative survival rates in relation to lymph node dissection in all patients (**a**); log rank test, $p = 0.10$ for D_0 , D_1 , and D_2), patients with stage I and stage II cancer (**b**; $p = 0.95$), and patients with stage III cancer (**c**; $p = 0.81$) [36]. There were no significant differences. D_0 = No lymph node dissection; D_1 = N_1 lymph node dissection; D_2 = N_2 lymph node dissection.

no differences have been observed over the past 20 years. Namely, no improvement in outcome has been observed after surgical treatment. On the other hand, in extensive radical pancreatectomies performed from 1991 to 2000 as the standard operation for pancreas cancer, the higher resectability was found to be more than 40%, in relation to the result of about 25% seen around 1980. But no significant improvement in survival rate has been seen.

Nakasako et al. [35] reported their experience with the extensive radical operation at one institute (186 cases) and no difference in 5-year survival was found: 7% during 1968–1979, and 8% during 1978–1995. Hirata et al. [36] and Mukaiya et al. [37] tried to analyze cases collected from multi-institutional experience. The effectiveness of extensive radical pancreatectomies was poor (fig. 2). On

Table 5. Number of cases with invasive ductal pancreatic carcinoma [1]

| Stage | Location | | | | Total |
|---------|----------|-----------|---------------------------------|-------|-------|
| | head | body-tail | head and body/ body and tail | whole | |
| I | 87 | 46 | 3 | 0 | 136 |
| II | 126 | 41 | 26 | 7 | 200 |
| III | 938 | 137 | 28 | 9 | 1,112 |
| IVa | 1,507 | 370 | 140 | 19 | 2,036 |
| IVb | 2,407 | 781 | 1,112 | 210 | 4,570 |
| Unknown | 1,019 | 346 | 342 | 76 | 1,753 |
| Total | 6,084 | 1,721 | 1,651 | 321 | 9,777 |

the other hand, Ishikawa et al. [2] and Nagakawa et al. [3] reported better results with the extended radical operation, and also Hiraoka et al. [38] showed the effectiveness of combination therapy with the intraoperative radiation added to the extended radical operation.

The 5-year survival of the stage I cases with pancreas head carcinoma was 56.7%, and that for cancer of the pancreas body and tail was 58.5%.

The high-quality prognosis in stage I suggested that the diagnosis of such small cancers should be required to in order to obtain better results in pancreatic cancer. However, the proportion of tumor size 1 cases and stage I cases among all cases were very low: 8.4% (table 1) and 1.4%, respectively (table 5).

The absolute number and proportion of small pancreatic cancers have gradually been increasing year by year, but advances in treatment methods have not kept pace. Therefore, most Japanese surgeons still often face extremely advanced cases of pancreatic cancer.

Based on expert opinion, the concept of the surgery was synchronous resection of the artery or portal vein, wide dissection of the plexus nerve and extended dissection of lymph nodes. This concept has recently been changed due to the data from the JPS registration system.

Extensive Radical Pancreatectomy versus Standard Pancreatectomy

Due to the extremely high incidence of histological non-curative results with standard dissection, extended radical dissection is used in pancreatectomy to prevent the frequent local recurrence which tends to occur in spite of a clinically curative operation. Extended radical dissection, which has major complications such as severe diarrhea, uncomfortable intestinal condition due to dissec-

tion of the plexus nerve, malnutrition and lower quality of life, continued to be of interest compared with the standard operation during the 1990s in Japan. Several Japanese reports on extensive dissection suggested the benefit of clearance of lymph nodes and retroperitoneal connective tissue [2, 3], which might have somewhat influenced this field in other countries. However, no significant difference between extensive radical and standard pancreatectomy was suggested by multicenter prospective randomized trials [39, 40] in Western countries, and the reason for this difference was not scientifically clear among Japanese surgeons. A difference in the background of the patients undergoing surgical treatment has been suggested. Western institutes with a record of relatively good prognosis have introduced low resectability, but most Japanese institutes with high resectability have not experienced an advance in post-surgical prognosis. For example, the highly advanced cases might be included more often in Japan than in Western countries. One retrospective study tried to address this issue [37], and indicated no survival advantage of extended dissection, except for a limited group of patients with a small number of microscopic lymph node metastases. No significant difference between extended and standard operations was found in an RCT study by Yeo et al. [39] in the USA and Pedrazzoli et al. [40] in Italy. The patients who received either the extended or standard operation had high rates of local recurrence and hepatic metastases, and they died. This poor prognosis may be due to the poor condition of the patients at operation who already had systemic disease. Nagino and Nimura [41] recently reported no statistical difference between the extended radical and standard operations for patients with stage II, III and IVa pancreatic cancer among Japanese patients by RCT. The result showed that the 1- and 3-year survival rates were 76.5 and 29.3% for the standard procedure, and 53.8 and 15.1% for the extended procedure. A slightly worse prognosis was suggested for the extended operation.

Accordingly, there is doubt about the significance of extensive dissection not only for advanced stages but also for earlier stages of pancreatic cancer.

In the near future, patients with or without indications for surgical treatment may be selected preoperatively according to the biological behavior of the cancer cells.

Indication of Vascular Resection

Nakao et al. [42] recommended extended radical resection for elective patients and concluded that the most important indication of this procedure is to obtain surgical cancer-free margins. There is no indication that the

Table 6. Portal and/or superior mesenteric vein resection in pancreatic cancer in Japan

| References | Patients | nPVR | Type of procedure | Year |
|-----------------------|----------|------|-----------------------------|------------|
| Mimura et al. [44] | 71 | 55 | PD:28, TP:27 | 1994 |
| Takahashi et al. [45] | 137 | 79 | PD:42, TP:32 | 1994, 1995 |
| Nakao et al. [46] | 200 | 146 | TP:69, PD:57, DP:9, PPPD:11 | 1995, 2001 |
| Imaizumi et al. [47] | 480 | 172 | Extend PD:150, Extend TP:22 | 1998 |
| Ishikawa et al. [48] | 43 | 27 | PD:27 | 1998 |
| Naganuma et al. [49] | 83 | 30 | PD, TP, DP, PPPD | 1998 |
| Shibata et al. [50] | 74 | 28 | PD:23, TP:3, DP:2 | 2001 |
| Kawada et al. [51] | 66 | 28 | PD:20, TP:5, PPPD:3 | 2002 |
| Aramaki et al. [52] | 69 | 22 | PD:14, TP:7, DP:1 | 2003 |
| Nakagohri et al. [53] | 81 | 33 | PD, DP | 2003 |

nPVR = Number of patients who underwent synchronous portal vein resection; PD = pancreatoduodenectomy; TP = total pancreatectomy; DP = distal pancreatectomy; PPPD = pylorus-preserving pancreaticoduodenectomy.

surgical margins will become cancer positive if extended resection is used in these patients.

Because of the absence of any RCT, Siriwardana and Siriwardana [43] made a detailed systematic review of outcome in patients following superior mesenteric vein (SMV) and/or portal vein (PV) resection during pancreatectomy. Japanese studies are shown in tables 6 and 7 [44–53]. Although regional pancreatectomy was recommended by Fortner [54] in 1974, this procedure is unfortunately associated with extremely high morbidity and no improvement in prognosis. Therefore, tumor extension to SMV/PV, superior mesenteric or celiac artery was recognized as a contraindication to surgical resection.

In 1996, Fuhrman et al. [55] reported no difference in hospital stay, morbidity, mortality, tumor size, margin positivity, modal positivity or tumor DNA content between two groups without or with SMV/PV resection. This study suggested that the development of SMV/PV resection was not significant and also that there is an inherent biological difference. However, when the purpose is to obtain cancer-free margins by PV/SMV resection, most Japanese surgeons would be eager to resect them simply for the low possibility of a good prognosis. Among those patients with systemic disease, only a few could be supported by adjuvant chemotherapy.

Effectiveness of Surgical Treatment for Advanced Pancreatic Cancer of the Pancreas

It has been discussed whether highly advanced but locally resectable pancreatic cancer can be adapted to surgical treatment or not. Imamura and Doi [56] faced this

Table 7. Morbidity, mortality and pathohistological results after portal and/or superior mesenteric vein resection in pancreatic cancer in Japan

| References | nPVR | Morbidity, % | Mortality, % | PV(+) % | RM(+) % |
|-----------------------|------|--------------|--------------|---------|---------|
| Mimura et al. [44] | 55 | | 11 | | 43.6 |
| Takahashi et al. [44] | 79 | | 9.5 | 61 | 38 |
| Nakao et al. [46] | 146 | | 5.5 | 71 | 58.2 |
| Imaizumi et al. [47] | 172 | 23 | 5 | 60.4 | |
| Ishikawa et al. [48] | 27 | | | 85.1 | |
| Naganuma et al. [49] | 30 | 16 | 1.2 | | 36.6 |
| Shibata et al. [50] | 28 | 32 | 4 | 58.3 | 29 |
| Kawada et al. [51] | 28 | 46 | 4 | 75 | 64 |
| Aramaki et al. [52] | 22 | 9 | 4.5 | 63.4 | |
| Nakagohri et al. [53] | 33 | | 6.1 | 51.5 | 24.2 |

PV(+) = Percentage of patients with portal vein involvement in surgical specimen; RM(+) = percentage of patients with resection margin-positive.

problem in a multicenter RCT comparing surgical resection and radiochemotherapy for locally advanced pancreatic cancer (limited strictly only to cases with JPS stage IVa). This study was performed using strict selection criteria, the final decision being made by direct observation and judgment during laparotomy after the preoperative diagnosis of stage IVa. It was concluded that such cancers, without involvement of the common hepatic artery or superior mesenteric artery, can be successfully treated by experienced surgeons at specialized centers, so-called

high-volume centers. Therefore, a substantial number of patients with stage IVa cancer still have curatively resectable disease and could have a more favorable outcome with surgery. Most skillful surgeons continue to resect stage IV tumors today.

No-Touch Isolation Technique

In order to prevent blood stream metastasis, the concept of isolated pancreatectomy [57] was created. With this aggressive procedure the patient undergoes bypass catheterization of the portal vein to decompress the congestion and prevent the shedding of cancer cells induced by the surgical manipulations of the pancreas head. Japanese reports on the incidence of pancreatic cancer cells in peripheral blood, bone marrow and liver tissue (table 4) have shown that this is the cause of distant metastases, which is supported by immunohistochemistry and molecular biological studies. Research has suggested the meaningful relationship between positive cancer cells in peripheral blood and distant metastases in cancer.

Kobayashi et al. [58] and Nakao and Takagi [57] suggested that the non-touch isolation technique (NTIT) could prevent liver metastases. During NTIT, isolation of the portal vein precedes ligation of the surrounding veins after dividing the duodenum and pancreas. Hirota et al. [59] proposed a different method of NTIT: ligation of Henle's gastrocolic trunk vein at the communicating point to the superior mesenteric vein, then division of the stomach or the upper duodenum, pancreas, choledochus, and jejunum. The pancreatic duct and choledochal duct should be ligated to prevent dissemination. Thereafter, the ligation of the portal vein branches follows. It is characteristic that no Kocherization is performed until all vascular branches are completed and no catheterization to the portal vein is needed. A comparative study of the NTIT and the conventional procedure with extensive intraoperative peritoneal lavage revealed: (1) the rate of molecular detection determines the rate of cancer cells in the portal venous blood and in the lymphatic fluid, and (2) the different frequency of hepatic metastasis, local recurrence and peritoneal dissemination. Further comparative study is necessary to confirm the significance of the NTIT procedure in pancreatic cancer surgery.

Mortality after Pancreatic Resection

Pancreatic resection is a high-risk surgical procedure with considerable postoperative morbidity and mortality. The hospital mortality rate after pancreatic resection has decreased during last 15 years, but there is a very wide variation in rates between institutes and countries. Re-

ports on the relationship between hospital volume and mortality after pancreatic resection provide a convincing evidence of an need for centralization, as several studies have assessed the impact of referral to high-volume centers on morbidity and mortality after pancreaticoduodenectomy [60–62]. Mortality rates at the high-volume centers are less than 5% and most reported less than 2%. Otherwise, centers with less experience continue to report mortality rates ranging from 7 to 15%. Birkmeyer et al. [61] reported the adjusted in-hospital mortality (1994–1999) among Medicare patients undergoing pancreatic resections: 16.3% (1 case/year), 14.6% (1–2 cases/year), 11.0% (3–5 cases/year), 7.2% (6–16 cases/year) and 3.8% (>16 cases/year). Therefore, Birkmeyer et al. [61] analyzed the summarized surgeon-specific and institute-volume outcome. Surgeon volume was divided into 3 groups: low (<2 cases/year); middle (2–4 cases/year), and high (>4 cases/year). Institute volume was divided into 3 groups: low (<3 cases/year); middle (3–13 cases/year), and high (>13 cases/year). Low-volume surgeons could have better results at higher-volume institutes. Further study is expected to clarify the influence of pancreatic condition on morbidity, i.e. parenchymal fibrosis and main pancreatic duct size and coexistent disease.

In some European countries such as the United Kingdom and Germany, centralization of institutes with a system of high-risk surgical procedures has been recommended, but its effects have not yet been analyzed and no precise report has been made [63]. It seems that the overall results are not changed. The data on hospital volume and mortality after pancreatic resection are too heterogeneous to perform a meta-analysis, but a systematic review shows convincing evidence of an inverse relation between hospital volume and mortality, and enforces the plea for centralization [64]. In Japan, there is no national registry concerning the outcomes of surgical treatment but the Japanese health insurance system is undergoing objective change which may lead to centralized systems. Cases will be optimized and medical costs minimized when patients with pancreatic cancer are referred to high-volume institutes.

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References

- 1 Pancreatic Cancer Registration Committee in Japan Pancreas Society. Pancreatic cancer registration of JPS: the summary for 20 years (in Japanese). *J Jpn Pancreas Soc* 2003;18: 101–169.
- 2 Ishikawa O, Ohhigashi H, Sasaki Y, Kabuto T, Fukuda I, Furukawa H, Imaoka S, Iwanaga T: Practical usefulness of lymphatic and connective tissue clearance for carcinoma of the pancreas head. *Ann Surg* 1988;208:215–220.
- 3 Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T, Ueno K, Miyazaki I: Results of extensive surgery for pancreatic carcinoma. *Cancer* 1996;77:640–645.
- 4 Takahashi S, Ogata Y, Miyazaki H, Maeda D, Murai S, Yamataka K, Tsuzuki T: Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. *World J Surg* 1995;19:653–659.
- 5 Nitecki SS, Sarr MG, Colby TV, van Heerden JA: Long-term survival after resection for ductal adenocarcinoma of the pancreas. *Ann Surg* 1995;221:59–66.
- 6 Sener SF, Fremgen A, Menck HR, Winchester DP: Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the national cancer database. *J Am Coll Surg* 1999;189: 1–7.
- 7 Trede M, Schwall J, Cameron J: Improved hospital morbidity, mortality and survival after the Whipple procedure. *Ann Surg* 1987; 206:358–365.
- 8 Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaïne F, Falconi M, Pedrazoli P, Pap A, Spooner D, Kerr DJ, Buchler MW: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350:1200–1210.
- 9 Kim HJ, Czischke K, Brennan MF, Conlon KC: Does neoadjuvant chemoradiation downstage locally advanced pancreatic cancer? *J Gastrointest Surg* 2002;6:763–769.
- 10 Klinkenbijnl JH, Jeekel J, Sahnoud T, van Pel R, Couvreur ML, Veenhof CH, Arnaud JP, Gonzalez DG, de Wit LT, Hennipman A, Wils J: Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg* 1999;230:776–784.
- 11 Takada T, Amano H, Yasuda H, Nimura Y, Matsushiro T, Kato H, Nagakawa T, Nakayama T: Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 2002; 95:1685–1695.
- 12 Ichikawa T, Haradome H, Hachiya J, Nitori T, Ohtomo K, Kinoshita T, Araki T: Pancreatic ductal adenocarcinoma preoperative assessment with helical CT versus dynamic MR imaging. *Radiology* 1997;202:655–662.
- 13 Oshikawa O, Tanaka S, Ioka T, Nakaizumi A, Hamada Y, Mitani T: Dynamic sonography of pancreatic tumors: comparison with dynamic CT. *AJR Am J Roentgenol* 2002;178: 1133–1137.
- 14 Saisho H, Yamaguchi T: Diagnostic imaging for pancreatic cancer, computed tomography, magnetic resonance imaging, and positron emission tomography. *Pancreas* 2004; 28:273–278.
- 15 Vargas R, Nino-Murcia M, Trueblood W, Jeffrey RB Jr: MDCT in pancreatic adenocarcinoma: prediction of vascular invasion and respectability using a multiphasic technique with curved planner reformations. *AJR Am J Roentgenol* 2004;182:419–425.
- 16 Scaglione M, Pinto A, Romano S, Scialpi M, Volterrani L, Rotondo A, Romano L: Using multidetector row computed tomography to diagnose and stage pancreatic carcinoma: the problems and the possibilities. *JOP* 2005; 13;6:1–5.
- 17 Glasbrenner B, Schwarz M, Pauls S, Preclik G, Beger HG, Adler G: Prospective comparison of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in the preoperative assessment of masses in the pancreatic head. *Dig Surg* 2000;17:468–474.
- 18 Kaneko T, Nakao A, Inoue S, Harada A, Nonami T, Itoh S, Endo T, Takagi H: Intra-portal endovascular ultrasonography in the diagnosis of portal vein invasion by pancreaticobiliary carcinoma. *Ann Surg* 1995;222: 711–718.
- 19 Sobin LH, Wittekind C (eds): International Union Against Cancer. TNM Classification of Malignant Tumors, ed 6. New York, Wiley-Liss, 2002.
- 20 Wray CJ, Ahmad SA, Matthews JB, Lowy AM: Surgery for pancreatic cancer: Recent controversies and current practice. *Gastroenterology* 2005;128:1626–1641.
- 21 Tada M, Omata M, Kawai S, Saisho H, Ohto M, Saiki RK, Sninsky JJ: Detection of ras gene mutations in pancreatic juice and peripheral blood of patients with pancreatic adenocarcinoma. *Cancer Res* 1993;53:2472–2474.
- 22 Inoue S, Nakao A, Kasai Y, Harada A, Nonami T, Takagi H: Detection of hepatic micrometastasis in pancreatic adenocarcinoma patients by two-stage polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) analysis. *Jpn J Cancer Res* 1995;86:626–630.
- 23 Nomoto S, Nakao A, Kasai Y, Harada A, Nonami T, Takagi H: Detection of ras gene mutations in peripheral blood with pancreatic adenocarcinoma. *Jpn J Cancer Res* 1996; 87:793–797.
- 24 Tamagawa E, Ueda M, Takahashi S, Sugano K, Uematsu S, Mukai M, Ogata Y, Kitajima M: Pancreatic lymph nodal and plexus micrometastases detected by enriched polymerase chain reaction and nonradioisotopic single-strand conformation polymorphism analysis: a new predictive factor for recurrent pancreatic carcinoma. *Clin Cancer Res* 1997;3:2143–2149.
- 25 Ando N, Nakao A, Nomoto S, Takeda S, Kaneko T, Kurokawa T, Nonami T, Takagi H: Detection of mutant K-ras in dissected para-aortic lymph nodes of patients with pancreatic adenocarcinoma. *Pancreas* 1997;15:374–378.
- 26 Funaki NO, Tanaka J, Hosotani R, Kogire M, Suwa H, Imamura M: Quantitative analysis of carcinoembryonic antigen messenger RNA in peripheral venous blood and portal blood of patients with pancreatic ductal adenocarcinoma. *Clin Cancer Res* 1998;4:855–860.
- 27 Aihara T, Noguchi S, Ishikawa O, Furukawa H, Hiratsuka M, Ohigashi H, Nakamori S, Monden M, Imaoka S: Detection of pancreatic and gastric cancer cells in peripheral and portal blood by amplification of keratin 19 mRNA with reverse transcriptase-polymerase chain reaction. *Int J Cancer* 1997;72: 408–411.
- 28 Miyazono F, Takao S, Natsugoe S, Uchikura K, Kijima F, Aridome K, Shinchi H, Aikou T: Molecular detection of circulating cancer cells during surgery in patients with biliary-pancreatic cancer. *Am J Surg* 1999;177:475–479.
- 29 Kuroki T, Tomioka T, Tajima Y, Inoue K, Ike-matsu Y, Ichinose K, Furui J, Kanematsu T: Detection of the pancreas-specific gene in the peripheral blood of patients with pancreatic carcinoma. *Br J Cancer* 1999;81:350–353.
- 30 Ishizone S, Yamauchi K, Kawa S, Suzuki T, Shimizu F, Harada O, Sugiyama A, Miyagawa S, Fukuda M, Nakayama J: Clinical utility of quantitative RT-PCR targeted to alpha1,4-N-acetylglucosaminyltransferase mRNA for detection of pancreatic cancer. *Cancer Sci* 2006;97:119–126.
- 31 Isaji S, Kawarada Y, Uemoto S: Classification of pancreatic cancer: comparison of Japanese and UICC classifications. *Pancreas* 2004;28:231–234.
- 32 Kawarada Y, Das BC, Naganuma T, Isaji S: Surgical treatment of pancreatic cancer. Does extended lymphadenectomy provide a better outcome? *J Hepatobiliary Pancreat Surg* 2001;8:224–229.
- 33 Smeenk HG, Tran TCK, Erdmann J, Eijck CHJ, Jeekel J: Survival after surgical management of pancreatic adenocarcinoma: does curative and radical surgery truly exist? *Langenbecks Arch Surg* 2005;390:94–103.

- 34 Matsuno S, Egawa S, Fukuyama S, Motoi F, Sunamura M, Isaji S, Imaizumi T, Okada S, Kato H, Suda K, Nakao A, Hiraoka T, Hosotani R, Takeda K: Pancreatic Cancer Registry in Japan: 20 years of experience. *Pancreas* 2004;28:219–230.
- 35 Nakasako Y, Hanyu F, Takasaki K: Indications for extended radical and pylorus-preserving Whipple operation for pancreatic cancer; in Hanyu F, Takasaki K (eds): *Pancreatoduodenectomy*. Berlin, Springer, 1997, pp 99–106.
- 36 Hirata K, Sato T, Mukaiya M, Yamashiro K, Kimura M, Sasaki K, Denno R: Results of 1001 pancreatic resections for invasive ductal adenocarcinoma of the pancreas. *Arch Surg* 1997;132:771–777.
- 37 Mukaiya M, Hirata K, Satoh T, Kimura M, Yamashiro K, Ura H, Oikawa I, Denno R: Lack of survival benefit of extended lymph node dissection for ductal adenocarcinoma of the head of the pancreas: retrospective multi-institutional analysis in Japan. *World J Surg* 1998;22:248–252.
- 38 Hiraoka T, Kanematsu K: Combined treatment of resection with intraoperative radiotherapy. Part 6: Tumors of the exocrine tissue: pancreatic cancer; in Beger HG, Warshaw AL, Buhler MW, Carr-Locke DL, Neoptolemos JP, Rusell C, Sarr MG (eds): *The Pancreas*. Oxford, Blackwell Science, 1998, pp 1085–1091.
- 39 Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH: Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma. 2. Randomized control trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002;236:355–368.
- 40 Pedrazzoli P, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, Kloppel G, Dhaene K, Michelassi F: Standard versus extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. *Ann Surg* 1998;228:508–517.
- 41 Nagino M, Nimura Y: Does ‘extended’ surgery for pancreatic head adenocarcinoma have survival impact? (in Japanese). *J Jpn Surg Soc* 2006;107:173–176.
- 42 Nakao A, Takeda S, Sakai M, Kaneko T, Inoue S, Sugimoto H, Kanazumi N: Extended radical resection versus standard resection for pancreatic cancer: the rationale for extended radical resection. *Pancreas* 2004;28:289–292.
- 43 Siriwardana HP, Siriwardena AK: Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatotomy for cancer. *Br J Surg* 2006;93:662–673.
- 44 Mimura H, Mori M, Hamazaki K, Tsuge H: Isolated pancreatotomy for ductal carcinoma of the head of the pancreas. *Hepatogastroenterology* 1994;41:483–488.
- 45 Takahashi S, Ogata Y, Miyazaki H, Maeda D, Mural S, Yamataka K, Tsuzuki T: Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. *World J Surg* 1995;19:653–660.
- 46 Nakao A, Kaneko T, Takeda S, Inoue S, Harada A, Nomoto S, Ekmel T, Yamashita K, Hatsuno T: The role of extended radical operation for pancreatic cancer. *Hepatogastroenterology* 2001;48:949–952.
- 47 Imaizumi T, Hanyu F, Harada N, Hatori T, Fukuda A: Extended radical Whipple resection for cancer of the pancreatic head: operative procedure and results. *Dig Surg* 1998;15:299–307.
- 48 Ishikawa O, Ohigashi H, Sasaki Y, Nakano H, Furukawa H, Imaoka S, Takenaka A, Kasugai T, Ishiguro S: Intraoperative cytodiagnosis for detecting a minute invasion of the portal vein during pancreatoduodenectomy for adenocarcinoma of the pancreatic head. *Am J Surg* 1998;175:477–481.
- 49 Naganuma T, Isaji S, Kawarada Y: Staging and extended resection for pancreatic cancer. *Pancreas* 1998;16:355–362.
- 50 Shibata C, Kobari M, Tsuchiya T, Arai K, Anzai R, Takahashi M, Uzuki M, Sawai T, Yamazaki T: Pancreatotomy combined with superior mesenteric-portal vein resection for adenocarcinoma in pancreas. *World J Surg* 2001;25:1002–1005.
- 51 Kawada M, Kondo S, Okushiba S, Morikawa T, Katoh H: Reevaluation of the indications for radical pancreatotomy to contraindication? *Surg Today* 2002;32:598–601.
- 52 Aramaki M, Matsumoto T, Etoh T, Ishio T, Himeno Y, Sasaki A, Yada K, Kawano K, Kitano S: Clinical significance of combined pancreas and portal vein resection in surgery for pancreatic adenocarcinoma. *Hepatogastroenterology* 2003;50:263–266.
- 53 Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S: Survival benefits of portal vein resection for pancreatic cancer. *Am J Surg* 2003;186:149–153.
- 54 Fortner JG: Regional resection of cancer of the pancreas: a new surgical approach. *Surgery* 1973;73:307–320.
- 55 Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, El-Naggar AK, Fenoglio CJ, Lee JE, Evans DB: Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. *Pancreatic Tumor Study Group. Ann Surg* 1996;223:154–162.
- 56 Imamura M, Doi R: Treatment of locally advanced pancreatic cancer: should we resect when resectable? *Pancreas* 2004;28:293–295.
- 57 Nakao A, Takagi H: Isolated pancreatotomy for pancreatic head carcinoma using catheter bypass of the portal vein. *Hepatogastroenterology* 1993;40:426–429.
- 58 Kobayashi S, Asano T, Ochiai T: A proposal of no-touch isolation technique in pancreatoduodenectomy for periampullary carcinomas. *Hepatogastroenterology* 2001;48:372–374.
- 59 Hirota M, Shimada S, Yamamoto K, Tanaka E, Sugita H, Egami H, Ogawa M: Pancreatotomy using the no-touch isolation technique followed by extensive intraoperative peritoneal lavage to prevent cancer cell dissemination: a pilot study. *J Pancreat* 2005;6:143–151.
- 60 Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, Welch G, Wennberg DE: Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137.
- 61 Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL: Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003;349:2117–2127.
- 62 Gouma DJ, van Greenen RCI, van Gulik TM, de Haan RJ, de Wit LT, Busch ORC, Obertop H: Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 2000;232:786–795.
- 63 Rosemurgy AS, Bloomston M, Serafini FM, Coon B, Murr M, Carey LC: Frequency with which surgeons undertake pancreaticoduodenectomy determines length of stay, hospital charges, and in-hospital mortality. *J Gastrointest Surg* 2001;5:21–26.
- 64 Van Heek NT, Kuhlmann KFD, Scholten RJ, de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ: Hospital volume and mortality after pancreatic resection. A systematic review and an evaluation of intervention in the Netherlands. *Ann Surg* 2005;242:781–790.

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