Interaction between Medical Treatment and Minimally Invasive Surgical Treatment for the Malignancies of the Digestive Tract

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Keywords

Gastric cancer · Colorectal cancer · Esophageal cancer · Digestive tract · Medical treatment · Minimally invasive surgery

Abstract

Recently, endoscopic diagnosis and treatment methods for early cancer in the digestive tract have made rapid progress. As for surgery, laparoscopic and thoracoscopic techniques have achieved rapidly advancing development in the last 2 decades. Early detection of the malignant lesion and the evolution of endoscopic and surgical device enabled in performing the minimally invasive surgery. Collaboration of medical treatment and minimally invasive surgery for advanced cancer is ongoing in the case of some conditions and in a few institutes. In this review, the contents of the core symposia on "Interaction between medical treatment and minimally invasive surgical treatment for the malignancies of the digestive tract", held at the 11, 12 and 13th annual meeting of the Japanese Gastroenterological Association, are summarized. At each annual meeting, the core symposium focused primarily on gastric, colorectal, and esophageal cancer treatment. For gastric cancer, endoscopic resection and laparoscopic surgery were 2 important key words.

For colorectal cancer, multidisciplinary therapy was a major key word. And for esophageal cancer, endoscopic resection, chemoradiotherapy, thoracoscopic surgery and salvage surgery were key words. Patients' survival and quality of life are expected to further advance as a result of the collaboration of such therapeutic modalities.

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Introduction

The Japanese Gastroenterological Association (JGA) organizes core symposia at its annual meetings in order to enable continuous discussion on several important topics. One of the topics is "Contact point between medical treatment and minimally invasive surgical treatment for the malignancies of the digestive tract". Recent advances in diagnostic imaging have made it possible to detect early cancers in the gastrointestinal tract, which could be cured by endoscopic treatments or minimally invasive surgery [1, 2]. On the other hand, limited surgery after multidisciplinary therapy (e.g., chemotherapy or chemoradiotherapy [CRT]) is one of the therapeutic strategies for treating locally advanced cancer. In this review, the contents of the core symposia are briefly summarized.

Forefront of Gastric Cancer Treatment (Core Symposium 1 at the 11th Annual Meeting of JGA)

Efforts are continually being made in both the fields of surgery and medicine to minimize the treatment invasiveness so as to reduce the risks associated with the treatment and improve the post-treatment quality of life (QOL) in patients with early gastric cancer.

In the field of endoscopic treatment, strip biopsy [3] and endoscopic mucosal resection (EMR) [4, 5] were introduced successively in the 1980s; however, both entailed the problem of high recurrence rates owing to the limited extent of en bloc resection possible and the ambiguity of the pathologic diagnosis based on piecemeal resection. Subsequently, laparoscopic local resection of the stomach was developed as a minimally invasive treatment in the field of surgery in the 1990s [6]. This operative procedure, consisting of endoscopic full-thickness resection of the gastric wall, was an epochal method in which, for the first time, endoscopy was performed in combination with laparoscopic surgery. The advent of endoscopic submucosal dissection (ESD) in the 2000s enabled en bloc resection of even extensive lesions [6], and subsequent improvements in the devices and techniques of local injections have led to the widespread use of this treatment technique [7–9]; also, there has been an increase in the application of this procedure for the treatment of early gastric cancer [10].

From the point of view of surgical treatment, laparoscopic gastrectomy with regional lymphadenectomy has come to be widely performed since the advent of laparoscopy-assisted distal gastrectomy [11]. Laparoscopic gastrectomy has been on the path of becoming a standard treatment for Stage I disease not only because of the smaller surgical wound in the case of abdominal surgery but also because of reduced pain, blood loss, and more rapid postoperative recovery [12–14]. It has also been shown that laparoscopy-assisted distal gastrectomy is in no way inferior to abdominal surgery in terms of the therapeutic results, even as an additional surgical procedure, in patients who have undergone a noncurative resection by ESD [15]. However, since the postoperative disorders are associated with gastrectomy or lymphadenectomy, the so-called small stomach symptoms of dumping and diarrhea can also occur after this procedure just as in the case of abdominal surgery, which is a next-generation organ-conserving reduction surgery, with focus on the long-term QOL.

Recently, medical-surgical collaboration that was aimed at precise excision of lesions while conserving as

much of the stomach as possible has led to the development of the so-called laparoscopic and endoscopic cooperative surgery (LECS) [16]. This method was, nevertheless, first devised for the treatment of gastrointestinal stromal tumors and has the drawback of being incapable of eliminating the risk of leakage of the gastric contents into the peritoneum upon opening of the stomach when it is applied for mucosal lesions, that is, for early gastric cancer. It is desirable to accomplish full-thickness resection of lesions without opening the stomach, as malignant cells could be suspended in the gastric contents even in cases of early gastric cancer [17]. In the 2010s, nonexposed endoscopic wall-inversion surgery (NEWS) [18] and a combination of laparoscopic and endoscopic approaches to neoplasia with the nonexposure technique [19] were introduced in succession as innovative LECS procedures and they are already being used in the treatment of early gastric cancer.

In the treatment of early gastric cancer, it should be noted that curability should not be impaired on account of overenthusiastic pursuit of minimal invasiveness, while bearing in mind that unnecessary resection of the lymph nodes may indeed give rise to postoperative disorders. A prospective multicenter clinical trial on sentinel node (SN) biopsy in patients with cT1N0/cT2N0 gastric cancer measuring ≤ 4 cm in diameter was reported in 2013, with the results demonstrating a high SN identification rate (98%) and a high lymph node metastasis diagnostic accuracy rate (99%) [20]. These results compare favorably with the results of SN biopsies performed on breast cancer or malignant melanoma patients with advanced SN navigation surgery, and suggest the possibility that typical lymphadenectomy could be at least reduced in extent or altogether omitted in SN metastasis-negative patients.

If it becomes practicable to accurately select cases of early gastric cancer without lymph node metastasis by SN navigation surgery in the future, indications for such procedures as total stomach-conserving ESD, LECS, non-exposed endoscopic wall-inversion surgery, and combination of laparoscopic and endoscopic approaches to neoplasia with the nonexposure technique could be further expanded. While the oncological curability and safety of the procedures should be cautiously assessed, it is expected that an ultimate minimally invasive treatment for early gastric cancer will be established, and furthermore, that the current trend toward individualized treatment will be hastened and established.

Forefront of Colorectal Treatment (Core Symposium 1 at the 12th Annual Meeting of JGA)

With prognostic comparison in the same stage, patients with rectal cancer have poor prognosis compared to colon cancer patients. A recurrent form of rectal cancer is characterized by local recurrence in addition to liver, lung, peritoneal dissemination, and lymph node recurrence. Therefore, control and treatment strategy for local recurrence is an important challenge for improving treatment outcomes of rectal cancer. To improve the outcome of rectal cancer treatment, preoperative concurrent CRT is performed in Europe and the United States, and lateral lymph node dissection (LLND) is performed in Japan.

Is an addition of CRT associated with minimally invasive treatment? The German rectal cancer trial group showed that sphincter preservation surgery was increasingly performed in patients needing abdomino-perineal resection [21]. In the pathological examination of the surgical specimen, intramural spread after CRT is of a low frequency and it is within about 1 cm [22]. It may contribute to expand the indication of sphincter-preservation surgery. However, as a disadvantage of CRT, the risk of anal dysfunction is increased [23]. There is a report showing that the postoperative anal function is decreased when the effect of preoperative CRT is strong in patients treated with intersphincteric resection [24]. Therefore, indication of sphincter-preserving surgery should be carefully decided. Another area that needs to be clarified is whether CRT achieves rectum preservation or not. In the GRECCAR2 trial [25], good clinical responders of CRT were assigned to local excision and rectal excision. Three-year overall survival and disease-free survival were almost the same in both groups.

In Japan, TME plus lateral LLND are standardized for T3 and T4 rectal cancer, and a satisfactory outcome is obtained [26]. Along with advances in systemic chemotherapy, neoadjuvant chemotherapy (NAC) is also being considered an attempt to improve the disadvantage of CRT. It is reported that NAC with oxaliplatin has high local effects like CRT and low frequency of lymph node metastasis [27, 28]. A comparison of CRT and NAC was carried out pathologically. The grade of reduction after preoperative CRT was more prominent than that in NAC. T factor downstaging was more prominent in preoperative CRT than in NAC; however, N factor downstaging was more frequent in NAC than in preoperative CRT [29]. As a large-scale clinical trial, the NCCTG N 1048 trial is now in progress, and a comparison between CRT and NAC will become clear in the future.

As for less invasive surgery, laparoscopic surgery is widely acceptable in treating early stage colorectal cancer. In JCOG0404 study, short-term surgical safety and clinical benefits of laparoscopic D3 dissection for stage II or III colon cancer were demonstrated [30]. Furthermore, survival outcomes following laparoscopic versus open D3 dissection were examined. Laparoscopic D3 surgery was inferior to open D3 surgery; laparoscopic D3 surgery could be an acceptable treatment option for patients with stage II or III colon cancer [31].

Colorectal cancer can be cured by metastatic resection even with distant metastasis. Even for distant metastasis, which is unresectable or marginally resectable, it is increasingly becoming resectable after chemotherapy. This strategy is named as conversion therapy. Several literature reports that chemotherapy with unresectable liver metastasis has made it possible to resect in 30–50% of patients and contributed to their prognoses [32–34]. Regarding addition of molecular target drug anti-EGFR agents, both response rate and resection rate were useful enough in the CELIM trial [35]. Also, a high response rate and resection rate by FOLF-FOXIRI regimen have been reported [36, 37]. Perioperative chemotherapy is being considered for resectable liver metastasis. In EORTC 40983 trial, prolongation of PFS is recognized, as compared with surgery alone, by performing FOLFOX with 6 courses before the operation and 6 courses after the operation [38]. Furthermore, in the new EPOC trial, it was investigated whether anti-EGFR agent was added to FOLFOX or CapeOX. Combination of anti-EGFR agent has been found to be without an additional treatment effect [39]. From analyzing hepatectomized patients, a nomogram was reported that can easily calculate the prognostic outcomes from 6 preoperative variables such as synchronous metastases, primary lymph node metastasis, number of liver tumors, tumor diameter, extrahepatic metastasis, and preoperative CA19-9 level [40].

In principle, hepatectomy is the first choice for topical treatment of liver metastasis, but there are reports in which radiofrequency ablation is used in combination to preserve residual liver volume. Results of radiofrequency ablation performed simultaneously with hepatectomy are slightly poor compared to the results of total liver tumor resection but are better than chemotherapy alone [41]. Although it can be considered a minimally invasive treatment for high-risk cases and cases of past-hepatectomy, as well as adaptation as cytoreduction combined with chemotherapy, it is a subject to be studied in the future. In future, further studies on combination of medical treatment and appropriate surgical treatment and personalized medicine are expected.

Recent developments in endoscopic technology have enabled to detect superficial esophageal cancer [42], and endoscopic resection represented by EMR and ESD is increasingly being accepted as a standard therapy for mucosal (T1a) esophageal cancer in Japan. On the other hand, the standard treatment for submucosal (T1b) cancer has been a surgical resection with adequate LLND because of the high incidence of lymph node metastasis (~40%) [43]. However, because the diagnosis of T1a or T1b is difficult in some cases, sometimes T1a esophageal cancer is treated by transthoracic esophagectomy and sometimes T1b is treated by EMR/ESD.

Transthoracic esophagectomy for T1a cancer is too much invasive because surgical resection often deteriorates patient's general condition. Therefore, especially for early stage esophageal cancer, thoracoscopic esophagectomy as minimally invasive surgery has become more popular among surgeons in an effort to preserve patients' QOL [44–46]. While there are many retrospective studies demonstrating the superiority of thoracoscopic esophagectomy to transthoracic open esophagectomy (OE), prospective studies are published from Western countries. The Eastern Cooperative Oncology Group (E2202) study demonstrated that minimally invasive esophagectomy (MIE; esophagectomy via the thoracoscopic and laparoscopic approach) is feasible and safe with low perioperative morbidity and mortality and good oncological result [47]. The TIME trial (traditional invasive vs. MIE, a multicenter, randomized trial) presented no differences in disease-free and overall 3-year survival for OE and MIE; therefore, this study supports the use of minimally invasive surgical techniques in the treatment of esophageal cancer [48]. In Japan, Takeuchi H et al. [49] compared short-term outcomes between OE and MI esophagectomy using the Japanese national clinical database. According to this study, operative time was significantly longer in the MIE group than that in the OE group, whereas blood loss was markedly less in the MIE group. MIE is beneficial in reducing postoperative respiratory complications. However, reoperation rate within 30 days was significantly higher in the MIE group than in the OE group. Based on these findings, a randomized phase III study (JCOG1409) was commenced to compare MIE with OE in terms of short-term and overall survival for stage I–III esophageal cancer [50].

A recent advance in techniques of EMR/ESD enables us to remove the clinical T1b tumor and gives us accurate diagnosis of depth of invasion [51]. However, the patients with T1b are at risk of lymph node metastasis and therefore, EMR/ESD alone cannot be considered curative. Therefore, surgical resection or CRT is added to pathological T1b tumor [52, 53]. CRT is thought to be less invasive than surgical resection, although it is the measure for late cardiac and pulmonary adverse events. Thus, the multi-institutional Phase II trial to evaluate the efficacy and the safety of combined treatment of EMR and CRT for clinical stage I (cT1bN0) esophageal cancer (JCOG0508) was carried out [54]. The outcome of this trial is favorable (3-year survival of all registered patients is 92.6%) and the strategy of additional CRT for cT1b esophageal squamous cell carcinoma according to the pathological findings after EMR/ESD may become a candidate of standard therapy because the survival rates are equal to those of esophagectomy.

As noted above, thoracoscopic esophagectomy and CRT must be regarded as minimally invasive treatments for noncurative cases after EMR/ESD for superficial esophageal cancer.

Recently, the practice of performing salvage surgery for the residue or recurrence after definitive CRT is increasing [55]. However, salvage esophagectomy is treated as a high-risk surgery because of high incidence of postoperative morbidity and mortality. For the improvement of short- and long-term postoperative superiority, many initiatives were undertaken. Thoracoscopic esophagectomy, transhiatal esophagectomy, lymphadenectomy without esophagectomy, and so on are reported as surgeries that constitute a minimally invasive salvage surgery. The success of a thoracoscopic and transhiatal salvage esophagectomy is based on the skill of surgeon, while they may be less invasive. For the common use of these surgeries, additional device and time will be needed. By the way, Watanabe M et al. [56] reported that patients with pre-treatment or preoperative T1–2 tumors and those with relapse after CR are good candidates for salvage esophagectomy based on both short- and long-term outcomes. Therefore, minimally invasive salvage esophagectomy may become the appropriate form of treatment for such patients in the near future. With regard to salvage lymphadenectomy, a favorable outcome is reported in some reports [57, 58].

Despite the restrictions of surgical region (mediastinal lymph node recurrence is hard to resect), it must be a promising minimally invasive surgery for selected cases.

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