

Chemoradiotherapy: Its Effectiveness, Toxicity, and Perspective in the Treatment of Esophageal Cancer

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Introduction

Many modalities of treatment have been developed to improve the therapeutic results of esophageal cancer, but this disease remains one of the most difficult cancers to cure. Radiotherapy is one such attempt. It has attracted huge attention since the concept of chemoradiation was introduced because of the improved response. Regarding all other modes of treatment, chemoradiation has merits and demerits, and its precise position in the strategy of esophageal cancer treatment is still under debate. This paper reviews the accumulated knowledge on chemoradiotherapy for esophageal cancer, and stresses with discussing its future direction.

From Radiotherapy to Chemoradiotherapy

Although radiotherapy for esophageal cancer treatment was introduced long ago, surgery has been regarded the standard treatment in Japan for resectable esophageal cancer, especially since Iizuka et al.¹⁾ reported negative results from preoperative radiation. Because of negative selection of radiotherapy candidates, the results of radiotherapy on esophageal cancer patients have remained very poor.²⁾ With the introduction of chemoradiotherapy (CRT),³⁾ however, its complete cure with organ preservation has become a reality. The promising results produced by Hironaka et al.⁴⁾ have advanced the concept of radical CRT for resectable esophageal cancer, and opinions such as “The first mode of treatment for esophageal cancer should be CRT. Surgery can be considered only for those who showed no sufficient response to it” have become prevalent.

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Toxicity of Chemoradiotherapy

After nearly 10 years that has seen an increasing number of reports on the risk of salvage surgery^{5,6)} and the long-term adverse effects of CRT,⁷⁻⁹⁾ surgery again has become the standard treatment. The difference between the actual results of the Japan Clinical Oncology Group (JCOG) 9906¹⁰⁾ and JCOG 9907,¹¹⁾ even though a direct comparison of these results has no statistical validity, has accelerated the trend back to surgery. Younger radiologists and oncologists now claim that there was no previous knowledge on the long-term toxicity of CRT. They claim that it became recognizable only after long survival with CRT was possible. But, is this correct?

Although CRT is a rather new treatment strategy, we accumulated vast experience using radiotherapy and its adverse effects in previous times when esophageal cancer was not a surgical disease and, later, when preoperative radiation was routine for it. Almost all older surgeons and radiologists have experienced necrotic bones; chronic skin ulcers; persistent pleural effusion; cardiac tamponade; damage to the spinal cord, to cardiac muscle, and to lung tissue; severe postoperative complications, and more. Therefore the idea of dose limitations was established through these difficult experiences. When the concept of CRT was introduced, all researchers were surprised by its increased effects, but they seem to have forgotten the possibility of a similar increase in adverse effects.

There have been many reports on the late adverse effects of CRT^{12,13)} from the early phase of its investigation. We have experienced several severe adverse effects, especially with patients in whom surgery and CRT were combined. Since then we have tried to minimize the dose of radiation when CRT is applied as a neoadjuvant or adjuvant treatment for surgery.

CRT with or without surgery is the most common treatment strategy for resectable esophageal cancer in Western countries, whereas surgery is the most common strategy in Japan. After JCOG 9907, the Japanese standard became a combination of neoadjuvant chemotherapy and

surgery. Neoadjuvant CRT is usually preserved for cT4 nonresectable tumors, and definitive CRT for resectable tumors is regarded as an alternative strategy adopted basically at the request of the patient. This situation is supported by the good results of esophageal surgery in Japan,¹⁴⁾ but also by the fear of surgeons to make neoadjuvant CRT a standard strategy added to the Japanese style of extensive radical operation.

New Trend in Chemoradiation Therapy

Recently a new CRT scheme was proposed by the Radiation Therapy Oncology Group (RTOG).¹⁵⁾ It consists of a chemotherapy schedule similar to conventional cisplatin (CDDP) and 5-fluorouracil (5-FU) and a reduced total dose (50.4 Gy), and also a reduced daily dose (1.8 Gy/d) of radiation using the multiple-field technique. Oncologists at the National Cancer Center East (NCCE) Hospital in Japan adopted this new scheme. According to their reports, this new CRT regimen is associated with the same complete response rate, lower long-term toxicity, and reduced operative risk when salvage surgery is demanded. Although the approvers of this new regimen are still in the minority among radiologists in Japan, we can accept CRT into our treatment strategy with more ease if this result is reproducible. Donahue et al.¹⁶⁾ and Tepper et al.¹⁷⁾ report that they use the new 50.4 RTOG regimen safely as neoadjuvant treatment for surgery. If such a strategy is possible also with Japanese-style radical esophagectomy, we can add one very important treatment choice to our menu to preserve the possibility of organ preservation maintaining the highest chance of cure. This notion is fascinating, but too early to accept because the radiation fields in Western reports are different from what we consider suitable, and more time seems necessary to admit the promising results of NCCE.

Toward the Future of Esophageal Cancer Treatment

From now on, the investigation to increase both the safety and the effectiveness of CRT will be one of the main topics for discussion in the field of esophageal cancer treatment, and to determine its precise position is now one of the most important clinical questions. We should not hasten to obtain the answer to this question because we have already realized good prognostic results with surgery; the real answer to the toxicity and safety of CRT requires more time. If careful observation can reach the conclusion that the revised CRT regimen is associated

with a high potential for cure and less adverse effects, allowing the acceptance of salvage esophagectomy with minimal risk, then the newer treatment strategy containing the new CRT regimen should be compared with the current standard strategy of neoadjuvant chemotherapy plus surgery, or with a similar strategy containing a newer set of anticancer agents. The ultimate goal is not to clarify which strategy has the higher potential for cure in the crude group of patients with resectable esophageal cancer, but to find in which patient which strategy is more suitable in terms not only of survival, but also of quality of life (QOL), including the chance of esophageal preservation.

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