Case Report

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Use of Intraoperative Radiotherapy in Pancreatic Cancer After Neoadjuvant Chemoradiotherapy: First National Application

Emin KÖSE[1], Servet Rüştü KARAHAN[1], Mustafa Halil AKBORU[2], Mustafa ÜNSAL[2], Ayhan ÖZSOY[1], Ahmet Cem ESMER[1]

[1]Clinic of General Surgery, Okmeydanı Training and Research Hospital, İstanbul, Turkey
[2]Clinic of Radiation Oncology, Okmeydanı Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Intraoperative radiotherapy (IORT) is a single fractional procedure performed during surgery in patients with pancreatic cancer. Its usage will increase in the future, particularly in abdominal disorders such as pancreatic cancer, in which prognostic outcomes are still poor despite technical improvements in radiotherapy and new drugs in chemotherapy. In this paper, we reported the case of a patient with pancreatic carcinoma localized in the junction of the head and body of the pancreas. After preoperative chemoradiotherapy (45 Gy radiotherapy with gemcitabine), distal pancreatectomy and splenectomy were performed and 12.5 Gy IORT was administered. The postoperative course was uneventful, except for a wound infection that was conservatively treated. A pathologic examination revealed resection of adenocarcinoma with negative surgical borders. The aim of this case report was to present the first IORT application for pancreatic cancer in Turkey. IORT can be used to decrease the possibility of microscopic residual disease in pancreatic tumors.

Keywords: Intraoperative radiotherapy, pancreatic carcinoma, gemcitabine

Introduction

Intraoperative radiotherapy (IORT) involves the application of radiotherapy (RT) during a surgical process. The goal of IORT is to enhance the local control by delivering radiation to the tumor site or to areas with potential residual microscopic disease, which have not been completely removed surgically. IORT is applied in a single session during the operation. Although IORT has a history of approximately a century, modern techniques began developing in the 1960s. Currently, IORT is still used in 16 countries and 90 centers (1). In Turkey, although IORT has been used in breast cancer cases in some centers, its application in pancreatic cancer cases has not yet been reported.

Abdominal organs have lower tolerance doses than those required for reducing tumors. A dose of 45–55 Gy RT, which can be administered at a conventional dose (1.8–2 Gy per fraction), is mostly not curative. Therefore, IORT administered during the operation helps in increasing the dose to curative doses and positively affects the responses and external RT does (1-3). In particular, in patients administered RT previously (those who received neoadjuvant or curative therapy but have recurrent disease), the additional dose must be administered as a single dose, possible only with IORT, to make the tumor site apparent and preserve healthy tissues, which can be affected because of their low tolerance doses, from radiation (1, 3). Although pancreatic cancer is rare, it is the fourth leading cause of cancer-related mortality (2). Surgery remains a component of treatment. Despite extended lymphadenectomy, newly developed chemotherapeutic agents, and RT, the local control and survival rate are not at the desired level. Therefore, IORT appears to be an appropriate choice for patients with pancreatic cancer.

Case Report

A 70-year-old female patient was admitted to our hospital with complaints of abdominal pain, weight loss, and vomiting that lasted for 3 months. She had a medical history of hypertension and had previously undergone total thyroidectomy, appendectomy, and cholecystectomy. The abdominal computed tomography (CT) of the

Address for Correspondence: Emin KÖSE; Okmeydanı Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye E-mail: dreminkose@yahoo.com

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patient revealed a mass, approximately 3´3.5 cm, at the caput-corpus junction, which was more hypodense than the parenchyma. It was observed that the mass covered arterial structures, particularly at the proximal segment of the splenic artery and at the level of the celiac trunk bifurcation, and it decreased their calibrations. A few lymph nodes smaller than 1 cm were detected at the level of the celiac trunk and the hepatogastric space in thin-section CTs. No view of any metastasis in the liver was observed (Figure 1).

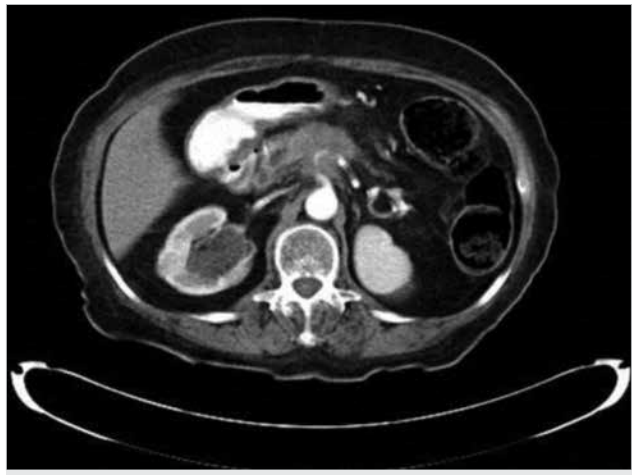

Figure 1. Preoperative computed tomography image

The patient was evaluated to have locally advanced pancreatic cancer, and she was included in the neoadjuvant chemotherapy program. The patient was given intensity-modulated RT at a dose of 45 Gy (25 fraction) with the linear accelerator device (Rapidarc©), and she underwent chemotherapy with 1400 mg gemcitabine in the pancreas and local lymph node. Abdominal CT taken after the treatment revealed regression in the size of the lesion, and no invasion was observed on evaluation of the celiac trunk. It was decided to perform resection. A 3.5-cm mass localized in the pancreatic corpus-cauda, showing invasion of the splenic artery but no invasion of the celiac trunk, was detected as a surgical finding (Figure 2). The patient underwent distal pancreatectomy and splenectomy and then, IORT. The IORT procedure was performed using the Mobetron© device, with a 6.5-cm applicator at zero-degree angle (4.5 cm tumor bed) and 1 cm bolus and emitting 12.5 Gy with 9 MeV electron energy (Figure 3). Infection developed at the wound site on the postoperative fifth day. It was treated through drainage and antibiotic therapy, and the patient was discharged on the 12th day. The pathological examination revealed a well-differentiated adenocarcinoma (4´2 cm) with perineural invasion, but no lymphovascular invasion. Ten reactive lymph nodes were detected in the peripancreatic adipose tissue, and the pancreatic surgical margin was found to be in good condition. Although the patient was administered prophylactic anticoagulant therapy for one month during the postoperative period, she was hospitalized due to pulmonary embolism that developed on the postoperative 40th day, which led to her death in the intensive care unit, despite the treatment.

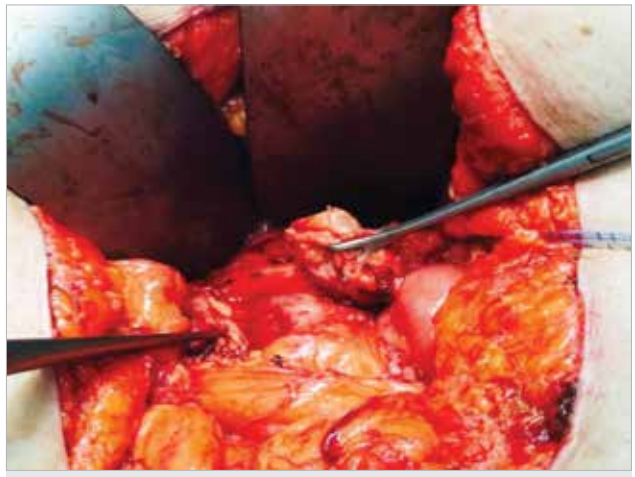

Figure 2. Association of the pancreas with adjacent organs

Figure 3. Mobetron device

Discussion

Despite all the developments in surgery, RT, and chemotherapy, pancreatic cancer remains to be one of the leading causes of mortality, and the treatment methods that have been applied remain non-promising. Surgical treatment is significant if good-condition surgical margins are obtained, and the patient has the advantage of survival only in this situation. The priority and order of components in combined treatments remain controversial. In USA, the standard approach in borderline pancreatic cancer is the use of 5-fluorouracil (5-FU) with external RT. It has been demonstrated that this regimen increases the survival rate by 6–9 months on an average (3). Although promising results have been obtained in recent studies conducted with gemcitabine instead of 5-FU (survival median, 11 months), it has not yet reached the desired level (4). With the development of stereotactic RT, comparative studies have been performed with the standard treatment arm (external RT+5-FU or gemcitabine) in these patients; however, no advantage of survival has been revealed. A single dose of

25 Gy was used only in the case series of Stanford University, and the survival median was reported to be 11.9 months (5).

If only IORT is used for non-resected tumors, 12–18-MeV electron energy is used for the target volume to be well covered. If radiation is to be delivered after resection, 9–12 MeV is sufficient. Applicators that will cover 1 cm additional area around the target should be chosen. In cases with a good-condition surgical margin or with microscopic residue, 10–12.5 Gy RT is sufficient. This dose should be increased to 15–20 Gy in the presence of macroscopic residue. In our case, the tumor bed was measured to be 4.5 cm after distal pancreatectomy. Considering potential microscopic residual disease, 12.5 Gy IORT was applied using 9-MeV electron energy with a 6.5-cm applicator. To reduce the dose for the spinal cord and to increase the isodose to the surface, 1 cm bolus was used. In studies using IORT with external RT, a limited number of health centers have reached prominence globally.

In the updated results obtained from the Massachusetts General Hospital, 150 patients receiving IORT with external RT+5-FU chemotherapy were examined, and long-term survival was determined in eight patients. While the median survival was found to be 13 months, 1- and 2-year survival rates were 54% and 15%, respectively. The survival rate was found to be significantly associated with the diameter of the applicator (and accordingly with the diameter of the tumor) (6).

In pancreatic cancer cases, a dose of 10–12.5 Gy of IORT is sufficient in the presence of R0 resection, after resection, or in the positivity of the microscopic surgical margin in patients who received 45–54 Gy RT previously. If there is macroscopic tumor residue, the dose to be delivered is 15–20 Gy. The dose can be increased up to 25–30 Gy when only IORT is planned, the patient has received RT previously, or the procedure is not planned to be performed during the operation. However, normal tissue (large veins and peripheral nerves) damage should be definitely considered. In the series performed by the Mayo Clinic researchers in Arizona in 26 patients using the protocol that we employed in our study, the median survival was found to be 19 months. The 2- and 3-year survival rates were reported to be 27% and 20%, respectively. (7).

The protocol used in the Japan series was 40 Gy external RT applied after 25 Gy IORT (8). However, survival rates in these studies are not as high as those in the Western series (median survival, 7.8 months).

Toxicity after IORT must be considered. As our patient had a tumor localized at the caput-corpus junction, distal pancreatectomy was performed, and the duodenum was left out of the site. Acute toxicities seen after IORT procedures have been found to be grade 2 and below in the European combined analysis. Surgical adverse effects include pancreatic fistula (27%), delayed gastric emptying (22%), bleeding (18%), repeated laparotomy (15%), abdominal abscess (14%), and sepsis (3%). Perioperative mortality was detected to be 2% (9). In our case, a wound site infection developed on the postoperative 5th day. It was thought that pulmonary embolism might have developed due to the existent malignancy and surgery in our patient because pulmonary embolism was not defined among early and late complications that could occur after IORT. In locally advanced and borderline pancreatic tumors, if there is no progression in the disease after neoadjuvant chemotherapy, surgical option should be reviewed again in selected patients with good functional capacity (10).

In conclusion, it can be suggested that IORT positively contributes to the local control of a tumor and can be used in selected cases, considering potential complications. However, attention should be paid to the selection of patients for this procedure. As observed in all new techniques, a certain time-period is needed to obtain a learning curve and experience on IORT. Although IORT is applied for breast cancer treatment in some centers in our country, no pancreatic cancer case treated with IORT has been reported yet. Our experience with IORT application in pancreatic cancer is the first case that has been reported in our country and new cases will be presented, undoubtedly. Our study will achieve its real potential as the number of patients increases and long-term follow-up results are obtained.

Informed Consent: We could not obtain informed consent because of patient's death.

Peer-review: Externally peer-reviewed.

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