Role of conversion surgery in patients with unresectable pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) continues to have a dismal prognosis, with a 5-year survival rate of <5%. Recent progress in chemotherapy has provided an improved median survival time (MST) in patients with unresectable PDAC from 6-8 months to 8.5-11.5 months. The treatment of unresectable PDAC is still a clinical challenge which may require a multidisciplinary approach. Recent chemotherapy provided the good response rates and the increased rate of conversion surgery in locally advanced PDAC as well as metastatic one. Previously, MST in patients with initially unresectable PDAC who underwent conversion surgery has been reported to reach 30-52 months. Moreover, a project study for pancreatic surgery by the Japanese society of hepato-biliary-pancreatic surgery (JHBPS 2013) revealed that the optimal time recommended for conversion surgery was more than 240 days after the initial treatment.

The conversion surgery in our institution was indicated in patients with tumor shrinkage, decreased tumor marker and good performance status (JHBPS 2014). The MST in 15 patients who were planned surgical resection was better than in 115 patients who did not have surgical indications (36 vs. 9 months, $p<0.001$). The mortality and morbidity rates in the study group were 0% and 46% respectively, in spite of concomitant organ resections in 77%. Thus, favorable performance of conversion surgery has been revealed but subjects of conversion surgery are mostly limited to the patients with locally advanced PDAC.

The prognosis of metastatic PDAC is extremely poor. Among them, the MST of patients with peritoneal metastasis (PM) has been reported to be 6-7 weeks only. The presence of PM may lead to intestinal obstruction, massive ascites, and malnutrition, resulting in poor performance status, which in turn deprives patients of the opportunity to receive chemotherapy. Compared to systemic chemotherapy, intraperitoneal (i.p.) chemotherapy appears to be advantageous for the treatment of PM due to the high drug concentration in the peritoneal cavity that can directly contact the tumor nodules due to their large molecular weight and fat solubility. Previously, it was shown that i.p.

paclitaxel (PTX) provided favorable clinical benefits in patients with PM in clinical trials of ovarian cancer and gastric cancer. Therefore, we introduced the i.v./i.p. PTX + S-1 combination therapy in chemo-naïve PDAC patients with PM. Most notably, our multicenter phase II study revealed a response rate of 36%, a conversion surgery rate of 24%, and an MST of 16.3 months in 33 chemotherapy-naïve PDAC patients with peritoneal metastasis. MST in 8 patients who underwent conversion surgery (27.8 months) was significantly longer than 14.2 months of 25 nonsurgical patients (p=0.0062, Ann Surg 2017). This regimen has shown remarkable performance, both in terms of the high conversion rate and the improved outcomes of patients with PM who underwent conversion surgery.

Thus, conversion surgery can be the important key to open the door for improving long-term survival in patients with unresectable PDAC. Sustainable efforts are warranted to explore the appropriate regimen of chemotherapy and measure of tumor remission, surgical indication, optimal time of conversion surgery, extent of surgical resection and so on.