Pancreatic cancer is still one of the most aggressive malignancies, showing 10% of 5-year survival. Among the several reasons of the grave prognosis, the poor response to chemotherapeutic agents and the absence of effective tool for early detection are the most important. Regarding treatments, surgical resection is still positioned as the only one for expecting the cure of pancreatic cancer. However, the rate of recurrence after surgery is still high as more than 50%. And the portion of patients who are diagnosed at the resectable stage is still less than 15% of all cases. So, chemotherapy and radiotherapy are the main players for combating with pancreatic cancer. After the introduction of outcomes of FOLFIRINOX, and gemcitabine/nab-paclitaxel for metastatic pancreatic cancer, two-digit overall survival can be expected. And, neoadjuvant treatments including concurrent chemoradiation therapy for borderline resectable pancreatic cancer and/or resectable pancreatic cancer are reported as superior to upfront surgery. More recently, several target agents including polyadenosine diphosphate-ribose polymerase inhibitors and immunologic drugs are under evaluation for pancreatic cancer. So, herein, current status of chemotherapy and radiation therapy for pancreatic cancer will be addressed.

INTRODUCTION

Pancreatic cancer is still one of the most aggressive malignancies, showing 10% of 5-year survival. The poor response to chemotherapeutic agents and the absence of effective tool for early detection are the most important reasons of the grave prognosis. Even though surgical resection is the only way to cure the disease, the number of patient suitable for surgery at initial diagnosis is less than 15% of all cases. And furthermore, more than 50% of the patients who received curative resection should enface recurrence of the pancreatic cancer. However, introduction of neoadjuvant therapy including chemotherapy and/or radiation therapy, surgical outcomes become better than before. And more effective chemotherapeutic regimens like...
FOLFIRINOX and nab-paclitaxel with gemcitabine can elongate the survival of advanced, metastatic conditions. More recently, several target agents including polyadenosine diphosphate-ribose polymerase (PARP) inhibitors and immunologic drugs are under evaluation for pancreatic cancer.

**MAIN BODY**

1. The role of chemotherapy

1) Adjuvant chemotherapy

Even with microscopically complete (R0) resections, recurrence rates are very high in pancreatic cancer. Therefore, additional adjuvant therapy is required for all patients with resected pancreatic adenocarcinoma. From early 1980s, there are several milestone studies for adjuvant chemotherapy of resected pancreatic cancer (Table 1). Especially, the European Study Group for Pancreatic Cancer (ESPAC-1) and CONKO (Charité Onkologie)-001 trial proved the benefit of adjuvant chemotherapy with gemcitabine or 5-fluorouracil (5-FU) plus leucovorin after curative surgery. In 2004, final data of ESPAC-1 was reported. They used 2x2 factorial design to randomize 289 patients to either chemotherapy with 5-FU/leucovorin or no chemotherapy, and chemoradiotherapy with 20 Gy dose in 10 daily fractions plus 5-FU or no chemoradiation. The overall survival of chemotherapy with 5-FU/leucovorin group was significantly better than no chemotherapy group (HR 0.71; 95% CI 0.55–0.92; p=0.009). With this study, adjuvant chemotherapy was turned out to be effective and beneficial. In 2007, Oettle et al. reported a randomized controlled trial-CONKO-001 with gemcitabine monotherapy versus observation after curative surgery. In this study, disease free survival was significantly longer in gemcitabine monotherapy group compared to observation group (13.4 vs. 6.9 months). However, median overall survival was comparable in both group (22.1 vs. 20.2 months). Based on this study, gemcitabine monotherapy has been regarded as one of standard adjuvant chemotherapy.

With the above data, adjuvant chemotherapy for pancreatic cancer was justified. There are still debates for what is the best regimen or a drug as adjuvant setting. In 2016, adjuvant S-1, an oral fluorouracil prodrug was evaluated for adjuvant chemotherapy with Japanese patients. In this study, S-1 showed remarkable superiority to gemcitabine monotherapy in overall survival (46.5 vs. 25.5 months, HR 0.57; 95% CI 0.44–0.72; p<0.001). Even though the authors concluded that S-1 rather than gemcitabine should be the standard adjuvant chemotherapy after surgery of pancreatic cancer, it should be validated for ethnic difference to S-1 in future. In 2017, the final data of ESPAC-04 trial was published. In this study, a total of 730 patients were randomized to adjuvant chemotherapy with gemcitabine ± capecitabine. The overall survival of gemcitabine/capecitabine group was 28.0 months and 25.5 months in gemcitabine monotherapy group (HR 0.82; 95% CI 0.68–0.98; p=0.032). More recently, the results from the multicenter, randomized PRODIGE24/CCTGPA.6 French-Canadian trial was reported. At a median follow-up of 34

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Control arm</th>
<th>Experimental arm</th>
<th>Median survival (months)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>43</td>
<td>Observation</td>
<td>5-FU/RT + 5-FU</td>
<td>10.9 vs. 21.0</td>
<td>0.03</td>
</tr>
<tr>
<td>ESPAC1</td>
<td>289</td>
<td>Observation</td>
<td>5-FU/LV</td>
<td>15.58 vs. 20.1</td>
<td>0.003</td>
</tr>
<tr>
<td>CONKO-001</td>
<td>368</td>
<td>Observation</td>
<td>Gemcitabine</td>
<td>20.2 vs. 22.1</td>
<td>0.06</td>
</tr>
<tr>
<td>ESPAC3</td>
<td>1,149</td>
<td>5-FU/LV</td>
<td>Gemcitabine</td>
<td>23.0 vs. 23.6</td>
<td>ns</td>
</tr>
<tr>
<td>JASPAC01</td>
<td>385</td>
<td>Gemcitabine</td>
<td>5-FU/LV</td>
<td>25.5 vs. 46.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESPAC-4</td>
<td>732</td>
<td>Gemcitabine</td>
<td>Gemcitabine/Capecitabine</td>
<td>25.5 vs. 28.0</td>
<td>0.035</td>
</tr>
<tr>
<td>PRODIGE/CCTGPA.6</td>
<td>493</td>
<td>Gemcitabine</td>
<td>mFOLFIRINOX</td>
<td>35.0 vs. 54.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 1. Summary of clinical trials of adjuvant chemotherapy for pancreatic cancer
months, disease free survival was significantly better with mFOLFIRINOX (21.6 vs. 12.8 months, HR 0.58; 95% CI 0.46–0.73; p<0.001), as was overall survival (54.4 vs. 35 months, HR 0.64; 95% CI 0.48–0.86; p=0.003).19

Based upon currently available data, gemcitabine ± capecitabine or mFOLFIRINOX can be considered as the first choice of adjuvant chemotherapy for the patients of resected pancreatic cancer. However, there is still a large proportion of patients with poor response to the above chemotherapy. So, pretreatment response prediction models for personalized treatment such as patient derived tumor organoids or conditionally reprogrammed cell culture should be more investigated.20

2) Neoadjuvant chemotherapy

As already mentioned, pancreatic cancer is notorious for high risk of recurrence after surgery even in cases of very early staged cancer. Furthermore, the potential risk of complications with relatively aggressive surgery such as Whipple’s operation frequently prevent the patient from receiving adjuvant chemotherapy. These situations are the reason why neoadjuvant therapy should be considered in specific situations of pancreatic cancer. However, because powered randomized trials are insufficient, long-term outcome of neoadjuvant therapy was found through phase II trials and retrospective database analyses (Table 2).

In resectable disease, it is examined, an observational retrospective study analyzed by propensity score matching in 15,237 patients with resected pancreatic cancer. It showed that those who received neoadjuvant therapy had better overall survival than those who received upfront resection (median survival 26 months vs. 21 months, respectively; HR, 0.72; 95% CI 0.68–0.78; p<0.01).21 Recently, SWOG S1505 trial is under way, which is a randomized phase II study intended to choose the most promising perioperative regimen (mFOLFIRINOX vs. gemcitabine/nab-paclitaxel [GnP]) for resectable pancreatic cancer.22 From 2015 to 2018, 147 patients were enrolled, but 42/147 (29%) were ineligible at central radiology review. Follow up for overall survival is ongoing.

In borderline resectable disease, whether neoadjuvant therapy is better than upfront surgery plus adjuvant chemotherapy, and what is the best regimens to use in the borderline neoadjuvant setting are debated topics. But several studies suggest that neoadjuvant therapy with FOLFIRINOX are an auspicious approach in patients with borderline resectable disease.23-25

3) Palliative chemotherapy

About more than half of the pancreatic cancer patients are diagnosed with metastatic disease. Consider unresectable status of locally advanced pancreatic cancer, more than two third of all pancreatic cancer patients should be treated with systemic anti-cancer therapies with palliative aims. But pancreatic cancer is one of the most resistant cancers to chemotherapy. It makes most novel drugs ineffective in so many clinical trials for pancreatic cancer. In real world, there are some auspicious signs for advanced pancreatic cancer such as introduction of relatively effective chemotherapeutic regimens or drug.

Table 2. Summary of clinical trials on neoadjuvant therapy with resectable pancreatic cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Therapy</th>
<th>Resection rate (%)</th>
<th>R0 rate (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer et al.19 (2007)</td>
<td>24</td>
<td>Gemcitabine</td>
<td>9/24 (38)</td>
<td>6/8 (75)</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Gemcitabine + Cisplatin</td>
<td>18/26 (70)</td>
<td>12/16 (75)</td>
<td>15.6</td>
</tr>
<tr>
<td>O’Reilly et al.20 (2014)</td>
<td>38</td>
<td>Gemcitabine + Oxaliplatin</td>
<td>27/38 (71)</td>
<td>20/27 (74)</td>
<td>27.2</td>
</tr>
<tr>
<td>Golcher et al.21 (2015)</td>
<td>33</td>
<td>Surgery</td>
<td>23/33 (70)</td>
<td>16/33 (48)</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>Gemcitabine/Cisplatin + Radiation</td>
<td>19/33 (58)</td>
<td>17/33 (52)</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Gemcitabine + Radiation</td>
<td>11/18 (61)</td>
<td>7/18 (39)</td>
<td>22.4</td>
</tr>
</tbody>
</table>
(1) First line chemotherapy
Since the report by Burris et al. in 1997, chemotherapy for advanced pancreatic cancer had the first turning point. In their study, gemcitabine monotherapy showed a modest survival gain over the treatment with 5-FU and clinical benefit in terms of pain relief and weight gain. The success of gemcitabine for advanced pancreatic cancer facilitated so many clinical trial based on combination therapy with gemcitabine. However, during the last 20 years, very few phase III trials showed positive data. NCIC CTG PA.3 trial showed that erlotinib (inhibitor of EGFR tyrosine kinase) plus gemcitabine was superior to gemcitabine alone, statistically significant improvements in overall survival (6.24 vs. 5.91 months; HR, 0.82; 95% CI 0.69–0.99; p=0.038), which is phase III, double-blind, placebo-controlled trial for 569 patients with advanced or metastatic pancreatic.27 Even though the survival gain is so marginal, this trial was the first study showing positive data with combination of gemcitabine and target agent.

In 2010s, two important studies provided another turning point in chemotherapy for advanced pancreatic cancer. In 2011, Conroy et al. reported results of the randomized phase III PRODIGE trial evaluating FOLFIRINOX vs. gemcitabine in patients with metastatic pancreatic cancer. The overall survival was 11.1 months in the FOLFIRINOX group and 6.8 months in the gemcitabine group (HR 0.57; 95% CI 0.45–0.73; p<0.001). Though, because of the higher rate of toxicity, it remains a treatment indicated for fit patients with good performance status. More recently, in 2013, Von Hoff et al. reported the data of phase III randomized clinical trial with GnP versus gemcitabine monotherapy for metastatic pancreatic cancer patients. They recruited 861 chemo-naïve patients with metastatic pancreatic cancer. The randomized trial showed that GnP was superior to gemcitabine alone in overall survival (8.7 months vs. 6.6 months; p<0.0001; HR, 0.72). In 2017, our group also performed retrospective cohort study to evaluate this combination for Korean patients because the MPACT trial included on 2% of Asian ethnic group. In our data, the median overall survival was 12.1 months and 8.4 months of progression free survival.

In terms of which is better between FOLFIRINOX and GnP, there is no direct comparative prospective data. However, recently, Cho et al. reported that there was no difference in survival gain (overall survival 10.7 in FOLFIRINOX vs. 12.1 months in GnP; p=0.157). The choice of first line treatment between both regimen should be based on not only the patient’s performance status but also the plan for the 2nd line or rescue therapy after failure of first line therapy.

(2) Second line or rescue chemotherapy
Although the advance in the first line chemotherapy for advanced pancreatic cancer, most of patients receiving the first line chemotherapy will be enfaced with cancer progression. So, rescue or 2nd line chemotherapy should be considered. However, there are very limited data for 2nd line chemotherapy for advanced pancreatic cancer. Before introduction of NAPOLI-1 trial, numerous small sized clinical trials were published. In 2014, the CONKO-003 phase III trial presented the OFF regimen including oxaliplatin, folic acid and 5-FU, as an effective 2nd line chemotherapy after gemcitabine refractory treatment, demonstrating significant improvement in overall survival when compared with 5-FU/leucovorin (5.9 vs. 2.9 months; HR 0.66; 95% CI 0.48–0.91; p=0.01). In 2018, our group also reported a single arm phase II study with modified FOLFIRINOX regimen for 2nd line chemotherapy. This study showed an acceptable toxicity profile and promising efficacy as a second-line treatment for gemcitabine-refractory unresectable pancreatic cancer. Total 48 patients were enrolled in this study, and the median PFS was 5.8 months (95% CI 3.7–7.9) and median overall survival was 9.0 months (95% CI 6.4–11.6).

In 2016, the NAPOLI-1 phase III randomized trial with patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy was reported. In this study, a total of 417 patients were randomized to receive the nanoliposomal irinotecan monotherapy, 5-FU/leucovorin, or both. Both of progression free survival and overall survival of nanoliposomal irinotecan with 5-FU/leucovorin group were significantly improved (progression free survival, 3.1 vs. 1.5 months; HR 0.56; 95% CI 0.41–0.75; p<0.001, overall survival, 6.2 vs. 4.2 months; HR 0.75; p=0.042).
2. Future’s perspective of chemotherapy for pancreatic cancer

1) Targeted therapies

Because of the heterogeneous environment of pancreatic cancer and complexity of stromal interactions, few targeted therapies succeed in clinical trials compared to standard treatment. As already mentioned, erlotinib plus gemcitabine was the only exception that showed statistically significant (2 weeks) improvement in overall survival.27 Although, most of the studies on targeted therapies failed during phase II/III trials, numerous phase I/IIb studies are still ongoing.

(1) PARP inhibitors

Up to 4% to 7% of pancreatic cancers arise in the setting of an inherited mutation in the breast cancer susceptibility (BRCA) 1 or 2 genes.33 In the POLO trial, 154 patients with germline BRCA-mutated metastatic pancreatic cancer that had not progressed during at least 16 weeks of first-line platinum-based chemotherapy were randomly assigned to olaparib (PARP inhibitors) or placebo.34 Maintenance olaparib was associated with a significant improvement in PFS (7.4 vs. 3.8 months; HR 0.53; 95% CI 0.35–0.82; p=0.004) than placebo. Based on these results, we now can consider olaparib as maintenance therapy for those with advanced BRCA or PALB2 germline-mutated pancreatic cancer who did not experience progression after initial platinum-containing therapy.

2) Immunotherapy including cell therapy, immune checkpoint inhibitor

Immune-checkpoint-inhibitor antibodies is a new treatment option, which inhibit the interactions between immune cells and antigen presenting cells, including tumor cells.35 One of immune-checkpoint-inhibitor antibodies, pembrolizumab, which blockades PD-1, may be susceptible in tumors with mismatch repair deficiency.36 Pembrolizumab, anti-PD-1 receptor antibody, blocks the interaction with its ligands, PD-L1 and PD-L2.36 And then, pembrolizumab improves antitumor immune response.36 It is showed that ORR was 62% among 6 pancreatic cancer patients in a phase II study in

Table 3. Select immunotherapy trials in pancreatic cancer64

<table>
<thead>
<tr>
<th>Category</th>
<th>Targets</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARP inhibitor + immunotherapy</td>
<td>PARP, PD-1, CTLA-4</td>
<td>NCT03404960</td>
</tr>
<tr>
<td>Chemotherapy + immune agonists and antagonists</td>
<td>Chemotherapy, CD40 agonist, anti-PD-1</td>
<td>NCT0324250</td>
</tr>
<tr>
<td>Anti-stromal drugs + immunotherapy</td>
<td>FAK, PD-1, FAK, PD-1, Gemcitabine</td>
<td>NCT02758587, NCT02546531</td>
</tr>
<tr>
<td>Matrix-targeted drugs + immunotherapy</td>
<td>PEGPH20*, PD-1</td>
<td>NCT03481920, NCT0319190, NCT03634332</td>
</tr>
<tr>
<td>Myeloid inhibitors + immunotherapy</td>
<td>PD-1, CSF1R*, PDLA, CFS1R*</td>
<td>NCT02526017, NCT02777710</td>
</tr>
<tr>
<td>Vaccines + immune checkpoint inhibitors</td>
<td>CRS-207*, PD-1, CTLA-4, GVAX</td>
<td>NCT03190265</td>
</tr>
<tr>
<td>Radiation + immunotherapy</td>
<td>PD-1, radiotherapy, PD-1, CTLA-4, radiotherapy</td>
<td>NCT02451982, NCT03153410</td>
</tr>
</tbody>
</table>

*PEGPH20, pegvorhyaluronidase alfa; CSF-1R, colony-stimulating factor 1 receptor; CRS-207, liver attenuated listeria-encoding human mesothelin vaccine; IDO, indoleamine 2,3-dioxygenase.
patients with 12 different mismatch repair deficiency advanced cancers, including pancreatic cancer. Even, 2 had complete response. Two major approaches affect to increase the impact of immunotherapy in pancreatic cancer, which are usually combined with chemotherapy. First, multitargeted strategies to stimulate antitumor T-cell responses are being studied. For example, in an ongoing clinical trial it is studied, a multi-drug regimen consisting of chemotherapy (e.g., GnP), CD40 agonist and anti-PD-1 (Table 3). In other strategies, the focus is on combining PD-1/PDL1 blockade with drugs that inhibit immunosuppressive mechanisms mediated by fibroblasts (e.g., FAK), matrix proteins (e.g., hyaluronidase), and myeloid cells (e.g., CSF1R, BTK CCR2, CXCR2) (Table 3). Second, immune based strategies are focused to enhanced responsiveness to chemotherapy. For example, CCR2 inhibitor which interrupts the immune-cell recruitment to tumors in the situation of cytotoxic stress, has shown effective activity in patients with locally advanced pancreatic cancer.38

As an immunostimulatory strategy for cancer therapy, radiation is combined with immunotherapy in pancreatic cancer (Table 3). Radiation has also affect increased expression of MHC class I on tumor cells and synergy with anti-CD40, anti-PD-1, and anti-CTLA-4.39,40

3. The role of radiation therapy for pancreatic cancer

In pancreatic cancer, radiation is usually used, concurrently combined with chemotherapy, gemcitabine- or fluoropyrimidine-based.41 Chemotherapy is used to increase the toxicity of radiation to tumor cells, as a radiosensitizer.41,42 To decrease local recurrence, radiation or chemoradiation are sometimes used for pancreatic cancer after resection. Radiation therapy (RT) in adjuvant or neoadjuvant settings has a goal to decrease local recurrence and increase the rate of a margin-negative resection, while minimizing the RT exposure to surrounding organs at risk.

1) Adjuvant chemoradiation

After resection, adjuvant RT may be considered in patients with a high likelihood of local recurrence (e.g., positive resection margins, lymph nodes).41,42 The role of radiation has not yet been clarified, and remains at studies.41 Updated 2020 guidelines from the NCCN suggest chemotherapy alone (FOLFIRINOX, Gemcitabine + nab-paclitaxel) as the preferred regimen for adjuvant therapy, but they include induction chemotherapy followed by chemoradiotherapy as an option for

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Group</th>
<th>Patients</th>
<th>Median survival time (months)</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG11-12</td>
<td>Chemoradiation (5-FU)</td>
<td>21</td>
<td>21</td>
<td>14 (5 years)</td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>22</td>
<td>10.9</td>
<td>4 (5 years)</td>
</tr>
<tr>
<td></td>
<td>Chemoradiation (5-FU) (additional)</td>
<td>30</td>
<td>18</td>
<td>46 (2 years)</td>
</tr>
<tr>
<td>EORTC65</td>
<td>Chemoradiation (5-FU)</td>
<td>110</td>
<td>24.5</td>
<td>51 (2 years)</td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>108</td>
<td>19</td>
<td>41 (2 years)</td>
</tr>
<tr>
<td>ESPAC-1 (pooled data)66</td>
<td>Chemoradiation (5-FU)</td>
<td>175</td>
<td>15.5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Chemoradiation (-)</td>
<td>178</td>
<td>16.1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (5-FU)</td>
<td>238</td>
<td>19.7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (-)</td>
<td>235</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>ESPAC1 (2×2)13</td>
<td>Observation</td>
<td>69</td>
<td>16.9</td>
<td>11 (5 years)</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (5-FU)</td>
<td>75</td>
<td>21.6</td>
<td>29 (5 years)</td>
</tr>
<tr>
<td></td>
<td>Chemoradiation (5-FU)</td>
<td>73</td>
<td>13.9</td>
<td>7 (5 years)</td>
</tr>
<tr>
<td></td>
<td>Chemoradiation + chemotherapy (5-FU)</td>
<td>72</td>
<td>19.9</td>
<td>13 (5 years)</td>
</tr>
<tr>
<td>RTOG 970444</td>
<td>5-FU chemoradiation</td>
<td>230</td>
<td>17.1</td>
<td>18 (5 years)</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine chemoradiation</td>
<td>221</td>
<td>20.5</td>
<td>22 (5 years)</td>
</tr>
</tbody>
</table>

Table 4. Randomized clinical trial of adjuvant chemoradiation therapy
adjuvant therapy.41 The Gastrointestinal Tumor Study Group has shown an advantage to adjuvant chemoradiation over observation after resection, but European Organization for Research and Treatment of Cancer reported no statistically significant differences between adjuvant RT and 5-FU versus observation, at median follow-up of 11.7 years.44 ESPAC-1 trial showed that adding radiation to adjuvant 5-FU chemotherapy may be rather harmful (Table 4).13,41

2) Neoadjuvant chemoradiation

Retrospective analyses found that neoadjuvant chemoradiation is better than neoadjuvant chemotherapy in local control, but not in survival.45 In resectable disease, although there is an evidence that neoadjuvant therapy may make a better chance of margin-negative resection,46 there are still few randomized trials. So, some randomized trials (SWOG 1505 trial [NCT02562716], or [NCT01389440]) are ongoing. Only patients, who have poor prognostic factors (e.g., significantly elevated CA 19-9; huge primary tumors; large regional lymph nodes; excessive weight loss; extreme pain) but appear resectable, can consider neoadjuvant therapy after biopsy confirmation.41

Recently, various kinds of radiation therapy were introduced. In RT modalities, there are stereotactic body radiation therapy (SBRT), intensity-modulated radiation therapy (IMRT), proton beam radiation therapy, charged particle therapy, and so on. First, SBRT, deriving from Gamma-knife, is advanced technique that increase dose to target while reducing exposure to surrounding healthy tissue.47-54 SBRT uses a variety of motion management techniques to account for tumor and normal tissue motion, permitting higher doses than conventional RT to the tumor while minimizing the risk of injury to adjacent organs. Retrospective study in the patients with locally advanced pancreatic cancer (n=998) represented that patients with SBRT compared to patients with conventionally fractionated RT had better median overall survival (13.9 vs. 11.6 months, respectively; p<0.001) and 2-year overall survival (21.7% vs. 16.5%, respectively; p=0.001).55 Also, IMRT, developed from 3-dimensional conformal radiotherapy (3D-CRT), is increasingly applied for treatment of locally advanced pancreatic cancer. In recent systematic review, IMRT was not superior to 3D-CRT at survival outcomes,56 but in IMRT, toxicities grade 3 or greater were fewer than in 3D-CRT (p=0.017). Besides, Proton beam radiation therapy is one of external beam radiation therapy, using not X-rays but proton beams. Proton radiotherapy can reach the optimal dose to targets while significantly normal-tissue sparing.57 Charged particle therapy is one of the most advanced technologies in radiation therapy.58 Charged particle therapy deposits more energy selectively, maximizing the effect on cancer and minimizing the damage from surrounding healthy tissue. And then, it can reduce complications and improve recovery rapidly after treatment.59

CONCLUSION

Although innumerable treatments have been developed, not many have been effective in pancreatic cancer. Since 1990, only 5 of over 30 phase III clinical trials involving 16,000 patients showed clinical benefit in terms of survival elongation. Chemotherapy is still the main therapeutic tool for pancreatic cancer, and in metastatic setting, FOLFIRINOX and Gem/nab-paclitaxel are the standard. As adjuvant chemotherapy, gemcitabine based treatment can be chosen as universally, and mFOLFIRINOX can be considered for patients with good performance status as adjuvant setting. In neoadjuvant setting, there are many things to be settled down including appropriate drugs or other modalities and definitions of the conditions. We look forward to a breakthrough in pancreatic cancer. Not limited to one treatment, precision medicine with different combinations of treatments should be more investigated in pancreatic cancer.

요 약

췌장암은 현재 가장 위험적인 약성종양 중 하나로, 5년 생존율이 10%밖에 되지 않는다. 이렇게 쌓아질 악성암의 예후가 불량한 데에는, 혈액학화학요법에 반응이 저조한 것과 초기 발견을 위한 효과적인 방법의 부재가 주요한 이유로 생각된다. 여러 치료 방법 중에서 수술적 치료만이 쌓아질의
Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES


