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Commentary

Do we need sequential local therapy following neoadjuvant chemotherapy for locally advanced pancreatic cancer?

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Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with an overall dismal prognosis. Although there has been progress in systemic therapies in the palliative and adjuvant setting [1], PDAC is predicted to be the second leading cause of cancer-related mortality within the next years. Surgery plus adjuvant therapy is currently the only option that offers a chance for cure in the small subset of patients that present with resectable tumors at the time of diagnosis. A relevant proportion of around 30–40% of patients present with borderline resectable or locally advanced, unresectable tumors. Resectability depends on the involvement of the venous and arterial vasculature, mainly the superior mesenteric vein, portal vein, superior mesenteric artery, celiac trunk and hepatic artery. Criteria and definitions of resectability have been defined and agreed upon internationally.

Especially for patients with borderline resectable or locally advanced, unresectable tumors, various neoadjuvant strategies have been proposed to convert unresectable tumors into resectable ones and/ or to increase the chance of microscopic tumor clearance (R0 resection) [1].

However, unlike in the palliative or adjuvant setting, high quality data from randomized controlled trials are mostly lacking, resulting in a variety of different regimens being used. Traditionally, especially in the era of ineffective chemotherapies, neoadjuvant protocols often included (chemo-) radiotherapy. However, with more effective chemotherapies being available, specifically FOLFIRINOX and Gemcitabine/nab Paclitaxel, there has been a shift towards chemotherapy rather than (chemo-) radiotherapy in this setting [1]. Starting with an effective systemic therapy makes clinical sense as pancreatic cancer is -in most cases- a systemic disease.

Several centers have reported resection rates of up to 60% in locally advanced, unresectable cases following neoadjuvant FOLFIRINOX therapy [2] and Gemcitabine/nab Paclitaxel [3], although there is substantial variation in how these patients are managed [4].

It is a matter of debate which patients should be considered for resection following neoadjuvant therapy. Most centers would advocate to explore all patients without disease progression, as response to therapy is often not reflected by imaging [5]. However, it has also been suggested that exploration should only be carried out after radiological response to induction therapy.

It is currently also a matter of debate whether patients should receive further 'local' therapy such as sequential chemoradiation following induction chemotherapy.

For example, Vidri and colleagues have shown in a retrospective cohort study that the addition of radiation to neoadjuvant chemotherapy resulted in a higher frequency of R0 resection rates and complete pathologic response, but rather strikingly had no effect on overall survival [6].

In another current phase II trial in 49 patients with untreated locally advanced unresectable pancreatic cancer, Murphy and colleagues demonstrated that neoadjuvant FOLFIRINOX with Losartan followed either by short- or long course chemoradiotherapy resulted in an 86% resection rate and a median overall survival of 31.4 months [7].

The LAPC-1 trial by Suker and colleagues published in *EClinicalMedicine* [8] is a phase II trial analysing sequential FOLFIRINOX (8 cycles) and Stereotactic Body Radiotherapy (SBRT, 40 Gy in 5 fractions) in patients with locally advanced pancreatic cancer. Primary outcome was 1-year overall survival, secondary outcomes were treatment related toxicity and resection rates among others. Fifty patients were included in the final analysis. 38% of the patients did not receive all 8 cycles of FOLFIRINOX due to toxicity or disease progression. 78% of patients received the assigned dose of SBRT, the other 22% did not receive SBRT due to progression or toxicity. Among the patients that completed both therapies, 10% showed local progression, 49% distant progression, and 10% both distant and local progression. The one-year overall survival rate was 64%. 12% underwent resection, all of them were R0 resected.

This well-designed trial adds further knowledge on the optimal neoadjuvant strategy in this challenging group of patients. It should be noted, however, that some cases of LAPC as defined in the current trial (according to the Dutch guidelines) would be borderline-resectable by the widely used international guidelines (ISGPS, NCCN).

Some aspects need to be highlighted. The resection rate of 12% is somewhat lower than reported rates for chemotherapy only in this group of patients. Resection rates as high as 60% have been reported. A recent meta-analysis summarizing 13 studies found a 28% cumulative resection rate [9]. An obvious positive effect on resection rates by the addition of SBRT can therefore not be concluded from this trial.

Only 10% of patients showed local progression; 49% distant progression and 10% both. While one could argue that these numbers point towards a positive effect regarding local tumor control for SBRT,

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the main dilemma remains: in most cases pancreatic cancer is a systemic disease that needs systemic control. It is questionable whether a potentially increased local control rate translates into a survival benefit or at least less symptoms and better quality of life for these patients. Third, a 5% mortality is possibly attributed to radiotherapy and no deaths were attributed to chemotherapy in the current trial. Although the overall numbers are small and have to be interpreted with caution, such mortality during therapy is substantial.

The aforementioned points do not strongly argue in favor of including SBRT in the treatment algorithm for locally advanced pancreatic cancer. In line with this, a randomized controlled trial (LAP07) did not reveal a survival benefit of chemoradiation (54 Gy plus capecitabine) compared to chemotherapy alone in LAPC patients following induction chemotherapy with gemcitabine or gemcitabine/erlotinib [10].

The conclusion that "FOLFIRINOX followed by stereotactic body radiotherapy for patients with locally advanced pancreatic cancer is feasible" is certainly justified. It remains to be seen whether there is a role of SBRT or any other local therapy following neoadjuvant chemotherapy in locally advanced pancreatic cancer. As of now, oncological surgery remains the 'local' therapy of choice in locally advanced pancreatic cancer patients that are stable following or respond to neoadjuvant chemotherapy.

Declaration of Competing Interest

All authors declare that there is no conflict of interest.

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