

## Neoadjuvant Treatment in Pancreatic Cancer: Where Are We?

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Pancreatic cancer is currently the 4th cause of death by cancer in Europe as well as in the US, where there have been 55,440 new cases and an estimated 44,330 deaths in 2018 [1]. Despite the different therapeutic strategies currently available, the overall 5-year survival remains 8% [2,3]. Moreover, due to complex extensions that the tumor can have, even when not metastatic, only 10 - 20% of the patient is eligible for upfront surgery with a 5-year survival raising to 10 - 30% [4]. The current trend for non-metastatic pancreatic adenocarcinoma is to differentiate three categories based on vascular involvement assessed by preoperative imaging: resectable (15%) [5], borderline resectable (20%) [6] and locally advanced disease (35%) [7].

Different strategies and combination of surgery and neoadjuvant and/or adjuvant therapies are currently investigated for those categories [8-10]. Although neoadjuvant therapy had shown beneficial effects for pancreatic cancer treatment, currently, treatment sequencing and specific elements of neoadjuvant treatment are still under investigation [4]. The benefit of a neoadjuvant approach may consist in select the patient with a less aggressive biological disease, control the micrometastasis and avoid the risk of drop-out from adjuvant treatment related to the post-operative complications and/or decline in the functional status [11-13].

Regarding resectable pancreatic cancer, the gold standard treatment is surgery followed by adjuvant chemotherapy [8]. Nevertheless, neoadjuvant treatment strategies are increasingly being employed for resectable pancreatic cancer [14-16]. Patients with resectable cancer who received neoadjuvant therapy revealed an overall survival of 23.3 months [17]. A Meta-analysis including 1056 patients with resectable disease have shown an overall survival of 30.0 (24.5 - 46) and 10 (9 - 11) months in resected and not resected patients respectively undergone Neoadjuvant [18]. Similar results have shown by two case series on patients treated with Gem+Ox (OS 27.2 months) or Gem+RT OS (22.7 OS months) [14]. In another study combining Gem with Cisplatin and RT the overall survival in 90 patients was 17.4 months [16]. Paclitaxel and docetaxel alone followed by RT were explored in two different studies showing 12 months OS [19] and 15.5 months OS, respectively [20].

The choice of neoadjuvant treatment for patients with borderline resectable pancreatic cancer is widespread. Several agents and combination were studied compared to upfront surgery. Gemcitabine single-agent use showed 2 years survival reached in 40,7% of the patients and OS of 21 months when compared to surgery (26.1% and 12 months) with an hazard ratio 1.495 (95% confidence interval 0.66 - 3.36) in an intention-to-treat analysis [21]. Another study analyzed FOLFIRINOX followed by gemcitabine/ capecitabine resulting in 22 months OS (range 18 - 35 months) [22].

The locally advanced disease consists in a tumor that contacts the superior mesenteric or hepatic arteries for more than 180°. That stage was formerly known as unresectable and it is considered inoperable. Less agreement is seen in literature regarding the infiltration of the superior mesenteric vein and the extent involvement and the celiac artery [23-25]. In a systematic review patients with locally advanced pancreatic cancer revealed an overall survival of 20.5 months if a resection was performed after successful neoadjuvant therapy

[17]. Several therapeutically approaches are available, however, the choice is mainly led by the patient performance status [26]. Although the systemic treatment can be given also with gemcitabine, nab-Paclitaxel, mFOLFIRINOX have become the standard of care [2,27]. In a recent systematic review and meta-analysis the median overall survival after neoadjuvant was 24.2 months (95% CI 21.7 - 26.8) [7].

Pancreatic Cancer is a lethal disease patient survival has not changed in the last forty years [28]. Neoadjuvant treatment has, recently, shown promising and encouraging results patients with Pancreatic Cancer. However, specific protocol and benefits at different disease stage are still under investigation, and high levels of evidence on specific neoadjuvant protocols are still missing [29]. Several international guidelines are recommending further RCTs to provide specific guidance for neoadjuvant treatment in Pancreatic Cancer, and the treatment should be performed in high volume centres with an interest in PaCa treatment [30,31].

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