REVIEW ARTICLE

Neoadjuvant Therapy in Pancreatic Cancer: Review Article

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ABSTRACT

Context Pancreatic cancer is still associated with a high mortality and morbidity for affected patients. To this date the role of neoadjuvant therapy in the standard treatment of pancreatic cancer remains elusive. The aim of our study was to review the latest results and current approaches in neoadjuvant therapy of pancreatic cancer. **Methods** We performed a literature review for neadjuvant therapy in pancreatic cancer. We divided the results into resectable disease and local advanced pancreatic cancer. **Results** Neoadjuvant therapy in pancreatic cancer is safe. But currently no standard guidelines exist in neoadjuvant approaches on pancreatic cancer. For local advanced pancreatic cancer the available data tends to show a positive effect on survival rates for neoadjuvant approaches. **Conclusion** For resectable disease we found no benefit of neoadjuvant therapy. The negative or positive effects of neoadjuvant treatment in pancreatic cancer remain unclear for the lack of sufficient and prospective data.

INTRODUCTION

Despite all efforts in developing better therapeutic strategies for the treatment of pancreatic cancer (PC), the disease remains fatal for the majority of patients. This is mainly due to the lack of diagnostic markers or symptoms, allowing a diagnosis at an early stage of the disease. Further complicated by an aggressive tumor growth, 50-80% of patients are diagnosed in a metastasized stage [1, 2]. The survival rates are measured in months rather than years and the average five year approximates 5 % [3, 4, 5]. Even after successful surgical resection with malignancy free margins does the five year survival rate not exceed 15-20% [6]. Since 90% of all pancreatic tumors are adenocarcinomas originating from the pancreatic duct system, most scientific studies have been performed exclusively on this tumor entity. All of the above are responsible for pancreatic cancer ranking number four in cancer realated deaths [7]. Because of its early systemic dissemination, pancreatic cancer should be managed as a systemic disease and an early systematic therapeutic approach close to the point of the diagnosis should be considered [8]. The surgical resection with microscopically free margins remains the single most important variable on the prognosis and the disease free survival in pancreatic cancer [9]. In order to further postpone the disease relapse, surgical intervention is generally followed by adjuvant chemotherapy. It is commonly accepted that any regime of chemotherapy should include a 6 month course of gemcitabine or 5-FU. Often neoadjuvant chemotherapy is combined with radiation of the tumor, occasionally even intraoperative radiation. Over the course of the last 15 years, neoadjuvant therapy has found its way into the therapeutic guidelines of many tumor entities, in the treatment of pancreatic cancer however, neoadjuvant therapy still remains not fully established. In this paper we give a short overview over the existing data on neoadjuvant approaches in the treatment of pancreatic cancer.

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METHODS

An online search with PubMed was performed for neoadjuvant therapy in pancreatic cancer which brought up numerous studies and opinion articles. The following search keys were used: “pancreatic cancer”; “neoadjuvant”, “preoperative”; “radiation therapy”; “chemoradiation”; “pancreas”; “pancreatic”; “adenocarcinoma” as well as the combination of these terms. Then by hand relevant studies were filtered by excluding opinion articles and case reports. All papers with meta analyses or review articles were included. A period of time from 1997 to 2014 was covered. We subdivided the analysis into resectable pancreatic cancer and locally advanced cases. We restricted results to pancreatic adenocarcinoma. The analysis did not vary whether the tumor was located in the pancreatic head, body or tail. Different operation techniques were also not taken into account. The aim was to give a short overview on the state of the art in neoadjuvant therapy of pancreatic cancer and inform the reader on new perspectives and developments in this field.

NEOADJUVANT THERAPY

As seen in other tumors e.g. rectal carcinoma, a neoadjuvant approach has become an essential part in optimal cancer therapy. Even though the idea is not new, the benefits of neoadjuvant therapy in the treatment of pancreatic cancer

therapy remain unclear. In the early 90's of the last century, the idea of a neoadjuvant concept for pancreatic cancer treatment was brought to life and has caused discussions ever since. As in other tumor entities, the difference between primary resectable and advanced tumor stage is crucial for the therapy process and influences the effectiveness of neoadjuvant therapy. Hence we decided to subdivide our review in these two categories.

Neoadjuvant Therapy in Resectable Disease

Resectable disease represents anatomically limited local pancreatic tumors, where surgical resection with malignancy free margins is possible. We found several studies and three meta-analyses investigating the effect of neoadjuvant treatment on primary resectable pancreatic cancer. The biggest series for neoadjuvant therapy in localized resectable pancreatic cancer came from MD Anderson cancer center (MDACC) [10-12]. They found higher rates of R0 resections, significant lower local recurrence rates and better survival rates among patients with resectable pancreatic cancer who showed no tumor progression under completion of neoadjuvant chemotherapy [13]. Greer *et al.* were able to confirm these findings. They reported a significant lower local recurrence rate, better survival rate and higher R0 resection rate for patients that underwent preoperative treatment and showed no disease progression, compared to patients without neoadjuvant therapy [14]. However some patients showed tumor progression under neoadjuvant therapy. MDACC could show that these patients do also not profit from subsequent surgical resection. In regard of choosing the right agent in chemotherapy, MDACC studies showed a significant benefit for gemcitabine in comparison to 5FU or paclitaxel [13]. Motoi *et al.* reported in a retrospective questionnaire based study significant higher rates of R0 resections in patients with resectable tumors who received preoperative treatment in comparison to patients with resectable disease and no neoadjuvant therapy [15]. Varadhachary *et al*. compared gemcitabine based combined neoadjuvant and adjuvant therapy with single adjuvant gemcitabine based therapy in a prospective phase II study [12]. They found no advantage in combined preoperative administered chemotherapy. In contrast a retrospective study within the Californian cancer surveillance program evaluated 458 patients with resectable disease. 8.5% underwent neoadjuvant treatment and showed better survival rates as well as a lower rate of lymph node involvement [16]. In 2012 Tajima *et al.* published a retrospective study which reported a significant better three year survival rate for patients receiving gemcitabine (plus oral sensitizer) preoperatively than in patients without neoadjuvant treatment and adjuvant therapy only [17]. Both groups showed a primary resectable state preoperatively. In a study of Kim *et al*. neoadjuvant therapy with gemcitabine and oxaliplatin was combined with radiation in patients with resectable tumors. They report an overall median survival of 18 months [18]. A study of Evans *et al.* which investigated the effect of gemcitabine based neoadjuvant radiochemotherapy in patients with resectable disease showed an overall survival rate of 23 months [19]. Brunner *et al.* initiated a randomized multicenter neoadjuvant phase II study with the help of the "Deutsche Krebshilfe" in 2007 for patients with resectable tumors. Patients are treated with gemcitabine/cisplatin based chemoradiation. The study is still enrolling and the results are not yet published [20]. In a very large meta-analysis of Gillen *et al.* 111 studies about neoadjuvant therapy in pancreatic cancer were investigated [21]. Better response rates were observed with radiochemotherapy than monochemotherapy. The actual resection rates in resectable tumors did not differ between patients treated with neoadjuvant therapy and patients with adjuvant therapy only in that study. Andriulli *et al.* also performed a meta-analysis and included 20 prospective studies where gemcitabine was administered preoperatively with or without radiation. They found only marginal benefits in survival for patients with initial resectable cancer [22].

Neoadjuvant Therapy in Locally Advanced Disease (Borderline, Non-Resectable)

To this day there is no commonly accepted definition of borderline resectable pancreatic cancer. The term should be seen as a part of locally advanced pancreatic cancer (LAPC) and non-resectable tumors. This continuum is changing rapidly in the last few years with better surgical techniques and higher resolution radiology imaging, which enables better diagnostic pathways and R0 resections in more and more patients. The essential factor to classify patients in the dimension of resectability is the tumor infiltration of the vascular axis in the upper abdomen. Callery *et al.* proposed a definition for the term borderline resectable in their paper of 2009 [23]. They stated borderline resectable tumors should have no distant metastases and in contrast to resectable states could show venous involvement of the SMV, portal vein and gastroduodenal artery encasement. In spite of the above, there still remains a great deal of division on the exact definition of the term. Initial staging of the patient in this continuum is vastly dependent on the expertise of the physician in charge. Most studies though evaluate LAPC as one group and therefore making it difficult to distinguish between borderline and initially non-resectable stages [24]. We found several smaller series and four review articles investigating the effect of neoadjuvant therapy in LAPC. In a review article including 21 studies Huguet *et al.* stated that in LAPC radiochemotherapy is not superior to single chemotherapy in terms of survival [25]. Motoi *et al.* investigated patients with borderline resectable tumors undergoing neoadjuvant therapy. They found no differences in R0 or mortality rates but higher blood loss and longer operation time as well as lower lymph-node involvement in patients with borderline tumors [15]. They also found no evidence for the potency of neoadjuvant treatment in downstaging borderline resectable tumors. In a prospective study of Leone *et al.* 39 patients with locally advanced pancreatic cancer were treated with neoadjuvant radiochemotherapy (gemcitabine and oxaliplatin). They saw higher progression free survival rates and an increase

of R0 resections [26]. In a meta-analysis of 2013 Festa *et al.* investigated 10 prospective studies of neoadjuvant treatment in patients with borderline resectable pancreatic tumors [27]. They could not see a significant increase in downstaging borderline resectable tumors during neoadjuvant treatment. The only benefit of neoadjuvant therapy was to identify patients with progressive disease under neoadjuvant treatment and eventually spare them surgical resection, from which they would not profit. In the meta-analysis of Andriulli [22] only a slightly positive effect of neoadjuvant therapy for a minority of those with non-resectable cancer was seen. Gillen *et al.* stated that one third of all initially non-resectable tumors could be restaged as resectable after neoadjuvant treatment, with similar survival rates as patients with initial resectable tumors [21]. In another meta-analysis of Assifi *et al.* 14 phase II Studies were analyzed with a total of 536 patients. They also found that one third of all tumors which initially where staged as non-resectable, could achieve a resectable status after neoadjuvant treatment [28].

DISCUSSION

This paper was intended to give a short overview on the role of neoadjuvant therapy in pancreatic cancer. The main-object is to enable more R0 resections, reduce lymph-node involvement and ensuring longer disease free survival and lower recurrence rates. Possible disadvantages of preoperative therapy may be the development of complications before cancer resection can be performed, such as biliary occlusion. This might cause a delay in surgical resection, resulting in a cancer progression to a non-resectable stage [17]. Before neoadjuvant treatment is initiated it is not possible to predict its effect on tumor progression for the individual patient. This means in some cases neoadjuvant therapy has no effect on tumor growth at all and therefore primary surgical resection may be the better choice [29]. MDACC showed that in these cases, there is no difference in survival rates between primary resection and neoadjuvant therapy. Additionally neoadjuvant treatment can help identify patients, who would not profit from surgery [10-12]. For these patients, by sparing them the struggle of surgery, one could provide a better quality of life. Over the course of the last 15 years, several studies have investigated the effect of preoperative treatment on resection and postoperative outcome [15, 30-32]. All of them showed no negative effects on postoperative complication or mortality rates for patients undergoing neoadjuvant cancer treatment In conclusion, neoadjuvant treatment does not seem to have any adverse perioperative effects on the outcome of patients suffering from PC and can therefore be regarded as safe [10, 33]. Possible advantages of neoadjuvant regimes lie within the ability to reduce perioperative tumor seeding [19] and the chance of decreasing the rate of lymph node metastasis [16, 29]. Several studies showed a decrease in lymph-node involvement and less node positivity during neoadjuvant therapy in LAPC disease [34, 35]. Since the involvement of lymph-nodes is a main predictor of survival [36, 37], it is comprehensible that neoadjuvant therapy seems to have a positive effect on survival rates in LAPC. The studies mentioned above are not uniform in that regard, but two big meta-analyses support the thesis of better survival rates for neoadjuvant therapy in LAPC [21, 28]. Other smaller series and one meta-analysis showed no positive effect of neoadjuvant therapy in LAPC. The problem with tumors initially graded as advanced is the definition itself. There are numerous different definitions and opinions on the exact grading of LAPC. This causes difficulties in interpreting and especially comparing the available studies, also in this review. Where possible we tried to group borderline resectable tumors and non-resectable tumors. 'Resection first' therapy bears the risk of a prolonged recovery period after surgery and therefore can produce delays in initiating adjuvant treatment or even prevent the patient from receiving adjuvant treatment [36]. Therefore neoadjuvant therapy may be sufficient to administer full cycle multimodal therapy to a greater part of affected patients [29]. Because unaltered vital tumor tissue is far more accessible for treatment than already altered tumor cells e.g. by surgery, preoperative therapy is supposed to gain better effects on tumor cells in contrast to therapy after resection [38, 39]. For initially resectable pancreatic cancer smaller series, including MDACC studies could show a positive effect of neoadjuvant therapy on R0 resection rates, survival and recurrence rates. It should be noted, that there was no direct comparison to patients with resectable disease and adjuvant therapy [10]. All available meta-analyses did not support these findings and showed no clear benefit for neoadjuvant therapy in resectable cancer [21, 22]. So for patients presenting with a non-resectable stage at the point of diagnosis it is reasonable to assess neoadjuvant treatment and enroll suitable patients in study protocols [18]. There is not much data about the question which agent or agent combination is the most effective choice in neoadjuvant therapy and which role radiation plays in that continuum. Available data seems to show no additional positive effect for chemoradiation in comparison to single chemotherapy [12, 18, 25]. Among all found studies during our literature research for this paper there is no large phase III Study. The reason for the lack of great multicenter studies may be due to the overall disagreement on exact patterns for neoadjuvant radiochemotherapy and/or exact definitions of resectability as well as the more appealing approach towards new agents in systemic cancer medicine via phase I and II trials [21]. With this in mind it seems legit that in recent guidelines on pancreatic cancer neoadjuvant approaches appear as only applicable in study regimes. Evidence collected so far depends on retrospective data and small case series that did not balance the different characteristics of patients suitable for surgery before or after neoadjuvant chemotherapy [8]. Furthermore no valid data exists for other tumor entities of the pancreas except for adenocarcinoma and no explicit data exists for tumors subdivided into anatomically regions of the pancreas such as head, body or tail.

CONCLUSION

Neoadjuvant treatment has a chance to improve survival in pancreatic cancer especially in patients with locally advanced disease and in detecting patients who most likely will not benefit from surgery. For resectable disease the available data seems to show no positive effect of neoadjuvant therapy. There is data from meta-analysis supporting the thesis that chemoradiation outperforms single chemotherapy in terms of survival [21]. An ideal treatment regime with therapeutic options available today has not yet been found. Phase III studies should be initiated to evaluate different neoadjuvant therapy modalities for pancreatic cancer, discriminating between resectable and LAPC disease.

Conflict of Interest

Authors declare to have no conflict of interest.

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