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Systematic or Meta-analysis Studies

The impact of neoadjuvant therapy on the histopathological features of pancreatic ductal adenocarcinoma – A systematic review and meta-analysis

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ABSTRACT

Background: Due to increased rates of curative tumor resections exceeding 60% after FOLFIRINOX-treatment, neoadjuvant therapy/NTx is increasingly recognized as an effective therapy option for down-staging borderline or locally advanced pancreatic ductal adenocarcinoma/PDAC. Yet, the effects of NTx on the common histopathological features of PDAC have not been systematically analysed. Therefore, the aim of the current study was to assess the impact of NTx on relevant histopathological features of PDAC.
Patients and methods: Biomedical databases were systematically screened for predefined searching terms related to NTx and PDAC. The Preferred-Reporting-Items-for-Systematic-review-and-Meta-Analysis/PRISMA-guidelines were used to perform a systematic review and meta-analysis. Articles meeting the predefined criteria were analysed on relevance, and a meta-analysis was performed.
Results: A total of 9031 studies could be identified that analysed the effect of NTx on PDAC. Only 35 studies presented comparative data on the histological features of neoadjuvantly treated vs. upfront resected PDAC patients. In meta-analyses, the beneficial effect of NTx was reflected by reduced tumor size (T1/2: RR 2.87, 95%-CI: 1.52–5.42, $P = 0.001$, T3/4: RR 0.78, 95%-CI: 0.69–0.89, $P = 0.0002$), lower N-Stage (N0: RR 2.14, 95%-CI: 1.85–2.46, $P < 0.00001$, N1: RR 0.59, 95%-CI: 0.53–0.65, $P < 0.00001$), higher R0-rates (R0: RR 1.13, 95%-CI: 1.08–1.18, $P < 0.00001$, R1: RR 0.66, 95%-CI: 0.58–0.76, $P < 0.00001$), less perineural invasion (Pn1: RR 0.78, 95%-CI: 0.73–0.83, $P < 0.00001$), less lymphatic vessel invasion (RR: 0.50, 95%-CI: 0.36–0.70, $P < 0.0001$) and fewer G3-tumors (RR 0.82, 95%-CI: 0.71–0.94, $P = 0.005$).
Conclusions: NTx in PDAC seems to exert its beneficial effect in borderline or locally advanced PDAC over genuine tumor downstaging. Thus, although at least 40% of all NTx treated patients remain unresectable even with modern NTx regimes, neoadjuvantly treated PDAC showed not only increasing resectability rates especially after FOLFIRINOX, but even reach a lower tumor stage than primarily resected PDAC.

Introduction

At the time of diagnosis, around 60% of all patients with pancreatic ductal adenocarcinoma/PDAC already have distant metastasis and advanced disease with invasion of arterial vessels or the celiac trunk [1]. Moreover, 30–40% of all patients have borderline resectable PDAC/BRPC with tumoral encasement of arterial vessels, so that they are also not eligible for primary surgery and often undergo palliative treatment or neoadjuvant therapy/NTx [2]. Therefore, curative therapy is only available for nearly 20% of all PDAC patients. Even after curative-intended surgery, 25% of resections end up in an incomplete, i.e. R1/2 resection [3]. Furthermore, several randomized controlled trials including patients treated with curative intention demonstrated failure rates of tumor therapy exceeding 70% [4,5]. Autopsy studies on patients, who were resected for PDAC, reported rates of distant metastasis and local recurrence reaching 75–88% [6,7].

NTx has dramatically changed the management of BRPC or locally advanced PDAC/LAPC cases [8–13]. Notably, NTx was shown to enable survival rates that are comparable to those of primary resected cases [14]. Moreover, in a recent study, Jing et al. reported that NTx decreases the frequency of local recurrence and therefore leads to better local control [8]. Importantly, perioperative

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morbidity and mortality does not seem to differ between patients with neoadjuvant treatment or with primary surgery [10]. However, due to a lack of randomized, phase-III-trials on the effect of NTx in patients with local resectable PDAC, the indication for NTx remains limited to patients with locally advanced or borderline disease [15].

The exact mechanisms behind the beneficial effects of NTx in locally advanced or borderline PDAC remain to be elucidated. In the past decades, several studies have demonstrated that NTx favourably affects various histopathological features of PDAC that are in general known to influence prognosis, such as tumor-positive margin status [16], tumor stage and grade [17,18], lymph node metastases [19], perineural invasion [20,21], and invasion into adjacent organs and structures [22,23]. Here, final pathology reports after NTx and surgical resection typically confirm the downstaging of the tumor, as reported by some studies in the past 5 years [12,13,24]. So far, a systematic review of the histological sites of action of NTx in PDAC has not yet been undertaken.

Therefore, in the current study, we performed a systematic review of the literature for the influence of NTx on the histopathological features in PDAC. Furthermore, we conducted a meta-analysis of studies comparing histopathological features of NTx-treated vs. upfront surgery PDAC patients and highlighted the impact of NTx in BRPC or LAPC.

Methods

Study design

The Preferred-Reporting-Items-for-Systematic-review-and-Meta-Analysis/PRISMA [25] were used to conduct this systematic review and meta-analysis. For this purpose, databases of Pubmed, Embase, Scopus and Google Scholar were systematically screened according the predefined search terms: "pancreatic cancer", "pancreatic ductal adenocarcinoma", "neoadjuvant therapy", "preoperative therapy", "neoadjuvant chemotherapy" and "neoadjuvant chemoradiotherapy". Additionally, the MESH-Terms "pancreatic cancer", "pancreatic ductal adenocarcinoma" and "neoadjuvant therapy" were used for screening of Pubmed. All studies on patients with PDAC that provided a comparison of histopathological features between neoadjuvantly treated patients followed by curative tumor resection and primary resected patients were included.

Data extraction

After removing duplicates, topics and abstracts were independently screened by two reviewers (SS and IED) for possible inclusion in the database of the systematic review. If inconstancy occurred during data extraction, studies were presented to two independent reviewers (GOC, HF). For study selection, the following inclusion and exclusion criteria were used:

1. Histological characteristics

Only publications with histologically proven PDAC were included in this study. Studies containing other solid tumors of the pancreas like cancers of the papilla Vateri, cholangiocellular cancers, adenosquamous cancers, neuroendocrine tumors, etc. were excluded. Furthermore, only studies containing exact numbers from histopathological reports were pooled in the meta-analysis. As a consequence, palliative patients with radiologically understaged PDAC or tumor progression during NTx were excluded from further analysis.

2. Characteristics of the studies

Importantly, only studies that directly compared the effect of NTx followed by curative resection with upfront surgery were included in the systematic review and meta-analysis. Consequently, studies that exclusively contained patients who all received neoadjuvant or adjuvant therapy, single-arm phase-I/II trails and all other studies comparing two different neoadjuvant therapy schemes without an upfront surgery arm, were also excluded from further analysis.

3. Study bias

To minimize the risk for double inclusion of patients' characteristics, only one trial per study group was included in our meta-analysis

4. Language

Only studies which were published in an English-speaking peer-review journal were eligible for this systematic review and meta-analysis. Reviews, systematic reviews, meta-analyses or studies published in other languages than English were consequently excluded but may be consulted for further studies.

After inclusion of relevant studies in the database of the systematic review, five independent reviewers (CMR, CS, ET, NS, RMS) screened independently all papers and extracted the data for meta-analyses. For this purpose, histological reports were screened for the exact of number of patients regarding T-stage, N-stage, G-stage, R-status, the incidence of neural invasion/Pn and of lymphatic invasion/Lyn. Afterwards meta-analyses were constructed by pooling the extracted data.

Subgroup analysis

To provide a more accurate insight into the true effect of NTx on the important histopathological features of PDAC, we decided to perform subgroup analyses. For this purpose, subgroup 1 included all studies which compared patients who were initially classified as resectable/RPC, BRPC, LAPC or unresectable PC/UPC and received NTx followed by curative tumor resection with patients who straightly underwent upfront surgery without NTx. Subgroup 2 comprised all studies that only included patients with resectable PDAC at primary staging who received upfront surgery or tumor resection after NTx.

Statistical analysis

Statistical analyses were performed with the Review Manager Software (Review Manager/RevMan, Version 5.3, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). In the meta-analysis, heterogeneity between the included studies was quantified using the inconsistency statistic (I^2). Study heterogeneity was defined as follows: If I^2 was 0, heterogeneity was absent is this study. If I^2 was less than 50%, a low level of heterogeneity was assumed. However, for both cases, the Mantel-Haenszel method for fixed effects was used to pool data. Furthermore, if I^2 exceeded 50%, a high level of heterogeneity was defined, and the DerSimonian method for random effect was used to perform meta-analyses [26], providing an estimate for an average risk ratio (RR). All results of the meta-analysis were expressed as pooled RR (95%-CI). To assess differences in harvested lymph node numbers between patients in the NTx and the upfront surgery group, all included studies of the meta-analysis of the impact of NTx on N-stage were screened for median numbers of harvested lymph nodes. Afterwards, the differences between the