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Chances, risks and limitations of neoadjuvant therapy in surgical oncology

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Abstract: Over the last decades, neoadjuvant treatment has been established as a standard of care for a variety of tumor types in visceral oncology. Neoadjuvant treatment is recommended in locally advanced esophageal and gastric cancer as well as in rectal cancer. In borderline resectable pancreatic cancer, neoadjuvant therapy is an emerging treatment concept, whereas in resectable colorectal liver metastases, neoadjuvant treatment is often used, although the evidence for improvement of survival outcomes is rather weak. What makes neoadjuvant treatment attractive from a surgical oncology viewpoint is its ability to shrink tumors to a smaller size and to increase the chances for complete resection with clear surgical margins, which is a prerequisite for cure. Studies suggest that local tumor control is increased in some visceral tumor types, especially with neoadjuvant chemoradiotherapy. In some other studies, a better control of systemic disease has contributed to significantly improved survival rates. Additionally, delaying surgery offers the chance to bring the patient into a better general condition for major surgery, but it also confers the risk of progression. Although it is a relatively rare event, cancers may progress locally during neoadjuvant treatment or distant metastases may occur, jeopardizing a curative surgical treatment approach. Although this is seen as risk of neoadjuvant treatment, it can also be seen as a chance to select only those patients for surgery who have a better control of systemic disease. Some studies showed increased perioperative morbidity in patients who underwent neoadjuvant treatment, which is another potential disadvantage. Optimal multidisciplinary teamwork is key to controlling that risk. Meanwhile, the neoadjuvant treatment period is also used as a "window of opportunity" for studying the activity of novel drugs and for investigating predictive and prognostic biomarkers of chemoradiotherapy and radiochemotherapy. Although the benefits of neoadjuvant treatment have been clearly established, the risk of overtreatment of cancers with an unfavorable prognosis remains an issue. All indications for neoadjuvant treatment are based on clinical staging. Even if staging is done meticulously, making use of all recommended diagnostic modalities, the risk of overstaging and understaging remains considerable and may lead to false indications for neoadjuvant treatment. Finally, despite all developments and emerging concepts in medical oncology, many cancers remain resistant to the currently available drugs and radiation. This may in part be due to specific molecular resistance mechanisms that are marginally understood thus far. Neoadjuvant treatment has been one of the major advances in multidisciplinary oncology in the last decades, requiring a dedicated treatment team and an optimal infrastructure for complex oncology care. This article discusses the goals and novel directions as well as limitations in neoadjuvant treatment of visceral cancers.

Keywords: chemoradiotherapy; chemotherapy; morbidity; mortality; neoadjuvant; respectability.

Introduction

The first attempts to establish neoadjuvant treatment for treating localized cancer date back to the 6th decade of the 20th century [1]. However, it was not before 40 years later that more adequately designed clinical studies for visceral cancers were carried out and published. Neoadjuvant treatment was done with the intention to shrink locally advanced tumors of borderline resectability. Investigators aimed to increase the probability of curative surgery. This goal was named "downsizing" or "downstaging". The American Joint Committee of Cancer Classification and the Union Internationale Contre le Cancer Tumor

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Node Metastasis (TNM) classification marked histopathological tumor stages following neoadjuvant therapy with the suffix "y" (e.g. ypT2 ypN1 M0) [2]. Chemotherapy was administered to shrink the primary tumor and to "eradicate" occult distant metastases. Radiation was administered to shrink primary tumors and to "sterilize" the tumor bed. Optimized combinations of both modalities were developed with the expectation of improving survival outcomes.

Local relapse rates were generally high in the early times of neoadjuvant therapy. This was probably a result of late diagnosis and suboptimal surgical care. Pioneer studies on neoadjuvant therapy reported increased curative resection rates [3] and dramatically improved local relapse and survival rates [4]. Meanwhile, staging has been refined by novel and more precise imaging techniques, including high-resolution computed tomography (CT), magnetic resonance imaging (MRI, sometimes complemented by specific contrast media and reading modes, e.g. diffusion-weighted MRI), endoscopic ultrasound (EUS), and metabolic imaging, especially positron emission tomography, applying tracers with different specificities, above all 18F-fluorodeoxyglucose. Better imaging led to a more accurate planning of surgical interventions. Surgical techniques continue to improve, and surgical quality control and auditing have been shown to improve surgical outcomes, including local relapse rates [5, 6]. Finally, radiation techniques and drugs used for neoadjuvant treatment are changing over time, leading to improved response rates and more favorable safety and toxicity profiles.

In summary, neoadjuvant therapy has become part of a curatively intended multidisciplinary treatment approach, in which surgery remains the mainstay of care. Neoadjuvant therapy remains a dynamic and evolving field of clinical research and application. This article outlines the chances, risks, and limitations of neoadjuvant chemotherapy in the present and gives an outlook into future developments.

Chances of neoadjuvant therapy

The chances and potential advantages of neoadjuvant therapy are summarized in Table 1. The upper part of the table displays achievements from prospective randomized controlled trials. These are outlined in more detail in Table 2. The lower part of Table 1 delineates evolving domains of neoadjuvant therapy, which will be discussed next.

In esophageal cancer, the latest studies and meta-analyses indicate a survival benefit for neoadjuvant chemotherapy as well as for neoadjuvant radiochemotherapy [18]. Although some studies suggest a greater benefit for neoadjuvant radiochemotherapy, others do not show a significant difference [19, 20]. Study details have been discussed in a previous paper [21]. However, recent results indicate that the R0 resection rate with contemporary chemotherapy regimens remains limited with neoadjuvant chemotherapy alone [22]. This observation has been used as an argument to emphasize the potential greater chances for neoadjuvant radiochemotherapy. For gastric cancer, the role of perioperative chemotherapy with regard to overall survival is supported by a high level of evidence coming from prospective randomized controlled trials [23, 24]. Whereas for rectal cancer, the role of neoadjuvant and/or adjuvant chemotherapy with regards to survival is unproven and discussed controversially [25], randomized studies clarified the value of neoadjuvant radiochemotherapy for a significantly better local tumor control, i.e. reduction of local recurrences [15, 16].

Table 1: Chances and potential advantages of neoadjuvant therapy.

Facts
– Increased complete resectability (R0) of the primary tumor
– Better local tumor control
– Lower distant relapse rates
– Improved survival rates (in some cancer types)
Chances
– Better feasibility of neoadjuvant versus adjuvant treatment
– Time for preoperative conditioning of the patient (nutrition, exercise, etc.)
– Potential for limited resection and organ preservation
– Potential for faster and more effective investigation of novel drugs and combinations

Other potential advantages of neoadjuvant treatment are less proven, as large-scale randomized controlled trials are lacking (Table 2, lower). However, it is clinically evident that in many cancer types, the administration of chemotherapy or radiochemotherapy is easier in the preoperative than in the postoperative phase. Of note, in the two largest perioperative chemotherapy trials for locally advanced gastric cancer, the rate for complete preoperative administration of chemotherapy was >90%, but it decreased to <50% in the post-operative phase [12, 13]. A recently published direct comparison of preoperative versus postoperative taxane-platin-fluoropyrimidine chemotherapy in gastric cancer confirmed this, showing that a higher dose intensity of chemotherapy was given in the preoperative study arm, whereas more chemotherapy-related serious adverse events occurred in the postoperative arm [26]. Also for radiochemotherapy in rectal cancer, fewer acute and long-term toxic effects have been shown for preoperative

Table 2: Clinical endpoints of recent prospective randomized controlled trials with an impact on the contemporary management of esophageal, gastric, and rectal cancer: comparison of neoadjuvant versus non-neoadjuvant treatment arms.

Study	Design	Complete (R0) resection rate	Local recurrence rate	Distant recurrence rate	Overall survival
Esophageal cancer					
OE2 [7, 8]	Preop. CTx vs. surgery	60% vs. 54%	11.9% vs. 12.5%	17% vs. 14.9%	5-year OS: 23% vs. 17% (HR 0.85; p=0.03)
CROSS [9–11]	Preop. RCTx vs. surgery	92% vs. 69%	34% vs. 14% (p<0.001)	35% vs. 29% (p=0.025)[a]	5-year OS: 47% vs. 33% (HR 0.67 [0.51–0.87])
Gastric cancer					
MAGIC [12]	Periop. CTx vs. surgery	69.3% vs. 66.4%	14.4% vs. 20.6%	24.4% vs. 36.8%	5-year OS: 36.3% vs. 23.0% (HR 0.75; [0.60–0.93]; p=0.009)
FNCLCC/FFCD [13]	Periop. CTx vs. surgery	84% vs. 74% (p=0.04)	12% vs. 8%[b]	30% vs. 38%[c]	5-year OS 38% vs. 24%; (HR 0.69; [0.50–0.95]; p=0.02)
EORTC 40954 [14]	Preop. CTx vs. surgery	81.9% vs. 66.7% (p=0.036)	Not reported	Not reported	2-year OS 72.7% vs. 69.9% (HR 0.84 [0.52–1.35]; p=0.466)
Rectal cancer					
Dutch TME [15]	Preop. RTx vs. surgery	94% vs. 93%	2-year recurrence 2.4% vs. 8.2% (HR 3.42 [2.05–5.71]; p<0.001)	2-year recurrence 16.8% vs. 16.8% (HR 1.02 [0.80–1.30]; p=0.84)	2-year OS 82.0% vs. 81.9% (HR 1.02 [0.82–1.25]; p=0.84)
AIO/ARO/ CAO-94 [16]	Preop. RCTx vs. postop. RCTx	91% vs. 90% (p=0.69)	5-year recurrence 6% vs. 13% (HR 0.46 [0.26–0.82]; p=0.006)	5-year recurrence 36% vs. 38% (HR 0.97 [0.73–1.28]; p=0.84)	5-year OS 76% vs. 74% (HR 0.96 [0.70–1.31]; p=0.80)
MRC CR07 [17]	Preop. RTx vs. postop. RCTX (in selected cases)	99% vs. 88% (p=0.12)	5-year recurrence 4.7% vs. 11.5% (HR 0.39 [0.27–0.58]; p<0.0001)	19% vs. 21% (no statistical comparison presented)	70.3% vs. 67.9% (HR 0.91 [0.73–1.13]; p=0.40)

CTx, chemotherapy; HR, hazard ratio; OS; overall survival; preop., preoperative; RCTX, radiochemotherapy; vs, versus; TME, total mesorectal excision; [] indicates the 95% confidence intervals. [a]Distant reported as hematogenous metastases. [b]Local relapse only. [c]Distant relapse only.

versus postoperative administration of the same regimen (Table 3). One of the advantages of neoadjuvant versus adjuvant radiochemotherapy is also the more precise anatomic definition of the target volume and easier protection of radiation-sensitive organs, compared with postoperative radiation. Recent evolutions in technology with intensity modulated and volumetric arc radiotherapy combined with functional imaging allows for an even better shaping of target volumes in the neoadjuvant setting.

The time during neoadjuvant therapy can and should be used to increase the patient's general health status. Impaired nutritional status is a particular problem in many patients with visceral cancers due to weight loss and digestion disorders in the months preceding the diagnosis of cancer. Perioperative nutrition has shown to enhance recovery after surgery [27, 28]. Recently published consensus guidelines of an international working group of Enhanced Recovery After Surgery recommend for patients who should undergo gastrectomy that "routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition before surgery" [29]. Recent prospective studies confirmed that preoperative malnutrition and weight loss are important predictors of poor clinical outcomes in patients undergoing gastrointestinal operations [30, 31]. Therefore, screening for malnutrition and nutritional counseling should be part of the neoadjuvant treatment concept.

A randomized and controlled pilot study [32], two non-randomized pilot studies [33, 34], and one retrospective cohort study [35] showed that an inspiratory muscle training before esophagectomy is feasible. Results from these studies suggest a reduction of postoperative pulmonary complications. This concept is now prospectively studied in the Dutch randomized and controlled 'Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection' (PREPARE) trial [36].

Reduced physical activity was shown to be a significant risk factor for pulmonary and other postoperative complications in patients undergoing esophagectomy [37, 38]. Consequently, the concept of preoperative

Table 3: Grade 3 or 4 toxic effects of radiochemotherapy in rectal cancer, according to actual treatment given, showing significant advantages for the preoperative versus the postoperative administration: data from the German rectal cancer study [16].

Type of toxic effect	Preoperative chemoradiotherapy (n=399)	Postoperative chemoradiotherapy (n=237)	p-Value
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long term			
Gastrointestinal effects[a]	9	15	0.07
Strictures at anastomotic site	4	12	0.003
Bladder problems	2	4	0.21
Any grade 3 or 4 toxic effect	14	24	0.01

Values are number of patients. [a]The gastrointestinal effects were chronic diarrhea and small-bowel obstruction. The incidence of small-bowel obstruction requiring reoperation was 2% in the preoperative-treatment group and 1% in the postoperative-treatment group (p=0.70).

conditioning by physical training during the period of neoadjuvant treatment is now studied in a prospective and oligocenter interventional trial in Germany [39].

An intriguing novel field is organ preservation or limited resection following optimal response to neoadjuvant therapy. This concept is challenging the old paradigm that said that the extent and radicality of surgery should always be the same, regardless of neoadjuvant therapy and response to neoadjuvant treatment. With regard to quality of life and functional status, these new approaches offer numerous potential advantages from the patients' perspective. However, oncological safety must be proven. What has already become standard of care for the treatment of localized breast cancer, based on compelling safety and survival data [40], requires careful evaluation and implementation in visceral oncology. For rectal cancer, careful selection of patients using high-resolution MRI may allow a non-surgical approach in a subgroup of patients achieving a complete response to neoadjuvant therapies after an adequate time period [41–43]. Clearly, this needs prospective evaluation within a clinical trial setting, incorporating modern imaging techniques, and tissue biomarkers to allow accurate prediction and assessment of response. The same concept is also followed in esophageal cancer, wherein a multicenter cohort study from French high-volume centers, salvage surgery suggests acceptable short- and long-term outcomes in selected patients [44].

Finally, the neoadjuvant treatment period offers an interesting "window of opportunity" to study new drugs and drug combinations. Assuming that response to neoadjuvant treatment, which can be assessed by anatomic imaging, functional imaging, or histopathology, is a reliable surrogate for drug efficacy, numerous studies have implemented novel drugs and combinations into neoadjuvant treatment of localized visceral cancers. Interesting response rates during neoadjuvant treatment may inform the design of consecutive confirmatory trials with survival outcomes as primary endpoint. However, a cautious note should be made: as long as survival data from controlled studies with a sufficient follow-up time are lacking, surrogate endpoints should not inform new standards of care.

Risks of neoadjuvant therapy

Although the benefits of neoadjuvant treatment are now clearly established, there are also risks that need to be considered and are still leading to discussions and some skepticism in the medical community. The most important ones are listed in Table 4.

With the current imaging tools, staging error is an inevitable and constant companion. This can trigger a false indication for neoadjuvant therapy. Understaging can lead to underuse, whereas overstaging can lead to overuse of neoadjuvant therapy. In general, the accuracy of preoperative staging is limited. Depending on the tumor entity, stage, diagnostic modality, and operator experience, inaccurate staging may occur in up to 25% of esophageal, gastric, or rectal cancers. One example is given in the European Organization of Research and Treatment of Cancer 40954 study for locally advanced gastric cancer, where the majority of enrolled patients was staged and treated in two German high-volume centers. Despite the use of meticulous staging procedures including EUS, CT scan, and extended diagnostic laparoscopy intended to limit enrollment to cT3–4 tumors, a large proportion of

Table 4: Potential risks of neoadjuvant therapy.

– False indication for neoadjuvant therapy based on staging error
– Overtreatment of tumors with a more favorable prognosis
– Deterioration of patients' performance status during neoadjuvant therapy
– Increased postoperative complication and mortality rates
– Tumor progression during neoadjuvant therapy
– Long-term side effects (including radiation-induced late toxicity)

patients in both arms were found to be pT2 without lymph node involvement at the time of surgery [14].

Based on the generally favorable results from randomized studies, some centers tend to extend the indication for neoadjuvant to lower stages of localized cancers. Of note, the evidence for efficacy in more favorable stages is scarce, as only a minority of study patients was included with low or intermediate tumor stages. Whether positive results from the trials can be extrapolated to patients with a more favorable tumor risk is unknown. A note of caution should therefore be raised. In a recent prospective randomized controlled study investigating the value of neoadjuvant radiochemotherapy in stage I and II esophageal cancer, neoadjuvant radiotherapy with concurrent cisplatin plus fluorouracil did not improve R0 resection rate or survival but enhanced postoperative mortality [45]. This study shows that the recommendations in which stages of local infiltration, extension, or nodal spread neoadjuvant treatment should be done remain challenging.

The chances for ameliorating the patients' physical condition during the time period of neoadjuvant treatment have been outlined above. In contrast, due to chemotherapy- or radiochemotherapy-induced toxicity, the patients' condition can also deteriorate. In some instances, very severe toxicity and even mortality during neoadjuvant treatment can occur. Treatment-associated (preoperative) mortality is assessed to be between 0.5% and 2% [39].

Some late and long-term side-effects have been attributed to neoadjuvant chemoradiotherapy. Pelvic radiotherapy is associated with an increased risk of late complications, including a substantial increase in bowel frequency and incontinence [46, 47] and delayed healing of the perineal wound when an abdominoperineal excision is done [48]. For rectal cancer, short-course radiation has been suspected to lead to more long-term side effects concerning sphincter and bowel function, but newer studies do not support this view. The finding of comparable long-term quality of life after short-course radiation and long-course-chemoradiotherapy adds to our knowledge of equivalent oncological outcome and may be useful in the decision-making process between the two neoadjuvant approaches [49]. Intensified neoadjuvant chemoradiotherapy portends a higher risk of long-term deterioration of "gastrointestinal quality of life" [49]. Future results of randomized trials investigating intensified neoadjuvant chemoradiotherapy versus conventional neoadjuvant chemoradiotherapy should be discussed in the light of long-term quality-of-life data [50].

Many retrospective epidemiological studies of second-cancer risks after radiation therapy have been conducted [51]. However, radiotherapy treatment techniques are changing quite rapidly, especially in terms of escalating treatment dose, altered dose fractionation, and altered normal-tissue dose distributions such as from intensity-modulated radiation therapy. Radiation-induced second cancers typically develop after a long latency period of a decade or more following exposure. For these reasons, risks estimated based on decades-old radiotherapy methods generally cannot be directly applied to modern or prospective protocols. Most studies lack long-term follow-up. Therefore, reliable numbers are missing. In view of the moderate doses used for neoadjuvant radiotherapy, the incidence of radiation-induced second cancers should be very low.

Although recent studies and meta-analyses do not indicate a major increased risk for postoperative morbidity and mortality following neoadjuvant chemotherapy or radiochemotherapy [52], some specific observations need to be taken into account. Following neoadjuvant radiochemotherapy of esophageal squamous cell cancer, significantly increased risk has been reported [52]. Although there was no significant difference in the incidence of complications between patients randomized to neoadjuvant chemotherapy or radiochemotherapy in a prospective randomized controlled trial in esophageal cancer, complications were significantly more severe after radiochemotherapy [53]. Additionally, neoadjuvant radiochemotherapy may increase the risk of severe anastomotic complications after esophagectomy with cervical anastomosis [54]. This, however, was not shown for other than cervical anastomotic leakages following esophagectomy [55]. In a cohort of patients undergoing total mesorectal excision for rectal cancer using current techniques, neoadjuvant radiotherapy was not associated with increased 30-day postoperative morbidity or mortality [56]. It is important to note that due to the growing center expertise with neoadjuvant treatment and improving radiation and surgical techniques and perioperative care, toxicity and complication risks vary and mostly decrease over time. This highlights that complex and multimodal treatment in visceral oncology should be performed at experienced centers only. The experiences from previous randomized

controlled trials regarding postoperative complications are summarized in Table 5.

Tumor progression during neoadjuvant treatment occurs, but the risk appears to be low, ranking from 1% to 5% (Table 5). One can argue that for patients who experience progression during neoadjuvant therapy, the chance for curative treatment was missed due to ineffective preoperative therapy. The more common view, however, is that progression during neoadjuvant therapy indicates a very aggressive tumor biology. Patients with such aggressive tumors may have never been good candidates for surgery and therefore may have been spared futile surgery. It remains to be elucidated which interpretation with regard to early preoperative progression is correct.

Limitations of neoadjuvant therapy

Despite important advances and positive study results for neoadjuvant treatment in visceral cancers, the neoadjuvant concept has also limitations (Table 6).

Until now, response rates to neoadjuvant therapy in visceral cancers are more or less disappointing. With available chemotherapy protocols, complete histopathological response rates in esophago-gastric cancer trials vary from only 4% to 15% [12, 13, 57]. With combined radiochemotherapy, better local response rates and local tumor control rates can be achieved. However, whether this leads to better overall survival is unproven; some studies have even been negative [16, 18, 20]. Better and more effective drugs are clearly needed, as it has been shown that giving more of the available drugs or giving the same treatment over longer treatment periods is ineffective [22]. Adding some of the novel biologically targeted drugs to neoadjuvant chemotherapy or radiochemotherapy has thus far been unsuccessful [58–61].

Future outlook

Response prediction and early response assessment during neoadjuvant treatment are evolving concepts aiming to tailor and individualize treatment according to response. Although early response assessment strategies are promising, they have thus far not been sufficiently validated in prospective multicenter studies [62–64]. Therefore, they should not be used outside of the context of quality assured clinical trials, which are difficult (if not impossible) to be funded. *Ex vivo* models to assess response to neoadjuvant therapy are being developed, but none of the models are ready for use in clinical practice [65].

Exciting new insights into tumor biology and molecular classification of the most important visceral cancers have been made available over the last couple of years [66–68]. These may serve as a roadmap for the development of the novel drugs and treatment strategies in the neoadjuvant treatment of resectable visceral cancers [69].

Finally, the expertise of a multidisciplinary team is key for good results of neoadjuvant therapy. All involved disciplines need to strive for optimal quality and must cooperate and communicate in an optimal way. We have

Table 5: Risks of neoadjuvant treatment: complications, mortality, and tumor progression in previous randomized controlled trials (neoadjuvant arm versus non-neoadjuvant arm).

Study	Postoperative complications	Postoperative mortality	Tumor progression during neoadjuvant treatment
Esophageal cancer			
OE2 [7, 8]	41% vs. 42%	10% vs. 10%	5/400 pts (1%)
CROSS [9–11]	Pulmonary: 46% vs. 44% Cardiac: 21% vs. 17% Chylothorax: 10% vs. 10% Mediastinitis: 3% vs. 6% Anastomotic leakage: 22% vs. 30%	4% vs. 4%	5/180 pts (3%)
Gastric cancer			
MAGIC [12]	46% vs. 45%	5.6% vs. 5.9%	Not reported
FNCLCC/FFCD [13]	25.7% vs. 19.1%	4.6% vs. 4.5%	3/113 pts (3%)
EORTC 40954 [14]	27.1% vs. 16.2%	4.3% vs. 1.5%	4/72 pts (5.5%)
Rectal cancer			
Dutch TME study [15]	No general differences reported	No general differences reported	Not reported
AIO/ARO/CAO-94 [16]	36% vs. 34%	0.7% vs. 1.3%	Not reported
MRC CR07 [17]	Anastomotic leak 9% vs. 8%	60-day mortality 3% vs. 3%	Not reported

Table 6: Limitations of the neoadjuvant treatment concept.

– Limited sensitivity of visceral cancers to available drugs and radiation
– Limited possibility of preoperative treatment intensification
– Difficult study designs due to multiple variables in multimodal treatment strategies

to work on the quality of our tumor boards, on rigorous quality assurance, and on patient orientation to achieve optimal results.

Author Statement

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Author Contributions

Writing of the manuscript: Florian Lordick; Revision of the manuscript: Ines Gockel and Florian Lordick; Approval of the manuscript: Ines Gockel and Florian Lordick.

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