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REVIEW

What is the impact of neoadjuvant chemoradiation on outcomes in gastro-intestinal cancer?

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Review

Summary Multimodal therapeutic strategies combining chemotherapy, radiation therapy and surgery have been shown to be feasible and to have a positive impact on outcomes by decreasing the risk of locoregional recurrence and often by increasing overall survival. The advantages of neoadjuvant chemo(radio)therapy include optimal tumor control combined with better tolerance and compliance to treatment while also increasing the number of candidates for surgery. Whereas indications for neoadjuvant therapy are increasing, its impact on surgical treatment and postoperative outcomes are not well-known. Surgeons frequently believe that chemo(radio)therapy may amplify intraoperative difficulties, thereby increasing postoperative morbidity and mortality. The aim of this review was to report the state of the art regarding: (i) the role of chemo(radio)therapy; (ii) its impact on surgical indications and modalities; and (iii) its impact on postoperative outcomes for the most frequently encountered gastro-intestinal cancers, *i.e.* esophageal, rectal, pancreatic, and anal canal cancer.

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Introduction

Patients with locally-advanced gastro-intestinal cancer treated by surgery alone are at high risk of locoregional recurrence and decreased overall survival. The association of chemotherapy, radiation and surgery as multimodal management has been shown to be feasible and to positively impact the risk of locoregional recurrence, and, frequently, to improve overall survival for several types of gastro-intestinal cancers [1]. Preoperative neo-adjuvant chemo(radio)therapy (NACRT) :

- allows application of these modalities to more patients since they are less well tolerated after surgery, or even sometimes, not performed in case of severe post-surgical complications;
- helps to avoid surgery in patients with tumors that progress despite NACRT and therefore to better select those patients who will most benefit from therapy;
- facilitates high-quality tumor excision thanks to down-sizing, thereby increasing the rate of complete (R0) resections;
- improves prognosis because down-staging deceases the risk of histologic lymph node involvement;
- increases the number of operable patients whose tumors were initially non-resectable because of adjacent organ involvement;
- contributes to assessment of tumor biology, particularly where the response to NACRT is used to guide adjuvant therapy;
- increases the efficacy of chemoradiotherapy (CRT) by its effect on the integrity of the peritumoral microvascularization.

While surgeons have a good understanding of surgical techniques and their outcomes, the impact of NACRT on the modalities of surgery and postoperative outcomes are less well known, and are often perceived as nocive, increasing operative difficulties and/or having a negative impact on postoperative outcome. The goal of this update was therefore:

- to revisit the rationale behind NACRT;
- to appraise its impact on the indications and the modalities of surgery;
- to evaluate its impact on postoperative outcome for five of the most frequently encountered gastro-intestinal cancers, esophageal, esophago-gastric, rectal, anal canal and pancreatic cancer.

Why perform chemo(radio) therapy before surgery?

In esophageal cancer

After surgery alone, 5-year survival for esophageal and esophagogastric cancers ranges from 33% to 41% [2,3]. Concomitant administration of neo-adjuvant chemotherapy and radiation therapy (based on 5-fluorouracil [5FU] and platinum or carboplatinum-paclitaxel in association with 41—45 Gy of radiation therapy) has been shown to improve overall and recurrence-free survival in patients with T3/T4 N0/N+ locally advanced esophageal cancer [4,5] and therefore constitutes the current standard management, especially for squamous cell carcinoma [1]. This scheme is still debated for locally advanced adenocarcinoma of the esophago-gastric junction, as its value has not been formally proven by the CROSS trial (hazard ratio after adjustment 0.75 [0.56—1.01], $P = 0.059$) [2], versus the alterative of perioperative chemotherapy. It has not been shown to be of value in less-advanced stages (T1/T2 N0/N+), where it was associated with increased postoperative mortality without any benefit on survival [3].

NACRT decreases primary tumor size (down-sizing), leading to increased R0 resection rates [4,5]. A down-staging phenomenon has also been described, achieving a complete histological response in 29—33% of cases [2,3]. This phenomenon is more frequently observed in squamous cell carcinoma than in adenocarcinoma (49% *vs*. 23%, $P = 0.008$) [4].

In sum, NACRT is validated for locally-advanced squamous cell cancer of the esophagus, but debated for adenocarcinoma depending on initial tumor resectability. For smaller tumors, it does not improve survival whereas postoperative mortality is increased.

In rectal cancer

NACRT is recommended in the management of mid-rectal and lower rectal T3 or N+ adenocarcinoma. This recommendation is based essentially on the results of two randomized trials:

- the first from Holland, comparing total mesorectal excision (TME) alone versus TME preceded by short course (5×5 Gy) radiation therapy found a 50% reduction in the risk of loco-regional recurrence at 3 and at 10 years in the combined therapy group although there was no difference observed in overall survival [6,7];
- the second, an European EORTC trial comparing preoperative radiation therapy alone *versus* NACRT, found a decreased risk of locoregional recurrence after NACRT, but once again, without any difference in overall survival between the two groups [8].

Since then, oral capecitabine chemotherapy was shown to be as effective as 5FU-Leucovorin [9] and three trials were unable to show that combined 5FU-oxaliplatin chemotherapy was better than 5FU alone [9,10]. The current standard neoadjuvant management for T3 or N+ rectal cancer is therefore NACRT with 50 Gy radiation therapy in association with oral capecitabine (CAP50).

In carcinoma of the anal canal

Almost all (80—95%) anal canal cancers are squamous cell carcinomas, and, in France, approximately 600 new cases occur annually. Anal carcinoma is a viral induced cancer due to *Human papilloma* virus (HPV), mainly HPV-16 infection of the anal mucosa. Before 1974, abdominoperineal resection (APR) was the standard treatment, often associated with inguinal lymphadenectomy; overall, survival ranged from 40—70% and morbidity was high. CRT subsequently became the standard therapy after several publications showed that concomitant CRT was superior to RT alone [11,12].

The choice of treatment depends on TMN status (Table 1). For T1N0 cancer, radiation therapy alone is indicated. For T2 (N0-N3) and T3-T4 (N0-N3) tumors, radiation therapy is associated with concomitant chemotherapy. Patients with metastatic disease should receive chemotherapy followed by radiation to increase local comfort. Chemotherapy consists of 5FU-mitomycin-C or 5FU-cisplatin associated with 25 fractions of 1.8 Gy (total: 45 Gy) radiation therapy. In patients who respond, a supplementary dose of 15—20 Gy

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