Human Pathology (2016) **52**, 164–172

ELSEVIER

Human PATHOLOGY

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Original contribution

Distal intramural and tumor spread in the mesorectum after neoadjuvant radiochemotherapy in rectal cancer: about 124 consecutive patients☆

Nathalie Guedj MD, PhD[a,*], Léon Maggiori MD[b], Nicolas Poté MD, PhD[a], Emma Norkowski MD[a], Jérôme Cros MD, PhD[a], Pierre Bedossa MD, PhD[a], Yves Panis MD, PhD[b]

[a]*Department of Pathology, Beaujon Hospital, 92110 Clichy, France*
[b]*Department of Colo-rectal Surgery, Beaujon Hospital, 92110 Clichy, France*

Received 20 August 2015; revised 15 January 2016; accepted 24 January 2016

Keywords:
Rectal cancer;
Radiochemotherapy;
Mesorectum;
Tumor deposits;
Lymph nodes metastases

Summary This observational prospective study aimed to assess the distribution of intramural and mesorectal tumor spread in mid/low rectal cancer after neoadjuvant radiochemotherapy. Distribution of mesorectal metastatic lymph nodes (MLNs) and mesorectal extranodal cancer tissue (EX), according to the tumor location, were analyzed. Distal intramural tumor spread was also performed. A total of 1676 LNs, 135 MLNs, and 69 EX were detected on 124 consecutive surgical specimens. Forty-two patients (34%) had MLNs. Six patients (4.8%) were classified as ypN1c. Distal viable cancer spread was observed in 3 patients (2.4%), all with mid rectal carcinoma. Two patients (1.6%) presented distal direct intramural extension less than 1 cm; and 1 (0.8%), with EX localized no more than 2 cm from the lower edge of the tumor. MLNs (76%) and EX (94%) were preferentially localized in the peritumoral area and in the first 3 cm just above the tumor. No viable distal intramural or mesorectal spread was observed in low rectal carcinoma. Distal intramural and mesorectal cancer spread is a rare event after neoadjuvant RCT. These results suggest that the 1-cm distal margin recommended in patients with low rectal carcinoma could be reduced with insurance to obtain a negative distal margin. The knowledge of preferential localization of MLNs and EX would help the pathologist to improve patient's lymph node staging.

1. Introduction

The introduction of total mesorectal excision (TME) as a surgical treatment for mid and low rectal cancer has led to major reduction in local recurrence rate from 30% to less than 10% [1]. Heald et al [2] first described that local recurrences were due to the presence of discontinuous mesorectal tumor

☆ Disclosures: All the authors state that there is no conflict of interest. The study did not receive funding.

* Corresponding author. Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy, France.
E-mail address: nathalie.guedj@bjn.aphp.fr (N. Guedj).

http://dx.doi.org/10.1016/j.humpath.2016.01.017
0046-8177/

foci, which were not removed with a conventional surgery and left behind in the pelvis. Thereafter, many investigators have described pathologic features of distal intramural and mesorectal cancer spread, which have been largely reported [3-10]. Based on these findings, the current National Comprehensive Cancer Network guidelines recommend a distal resection margin of 4 to 5 cm for partial mesorectal excision and 1 to 2 cm for TME [11]. However, TME is associated with a high occurrence of morbidity including anorectal and urogenital dysfunctions, probably due to the low anastomosis generated by TME [12,13].

Neoadjuvant radiochemotherapy (RCT) has recently complemented the therapeutic management of locally advanced mid/low rectal cancers. It demonstrated an improvement of local recurrence rate, significant tumor downstaging and a pathologic complete tumor response (pCR) in 10% to 30% of patients [14-17]. In addition, neoadjuvant RCT may result in sphincter preservation for low rectal carcinoma and may allow to consider a simple local excision or a "wait and see" policy in very selected patients [18], leading to a better quality of life.

Few studies have investigated the impact of neoadjuvant RCT on intramural and mesorectal tumor spread [19-23]. We wanted to know if neoadjuvant RCT modified their rate and their distribution and if these new distributions could have an impact on current surgical recommendations still based on outdated studies performed before the advent of neoadjuvant RCT.

Then, the purpose of our study was to examine the incidence, the distribution, and the modes of intramural and mesorectal cancer spread in rectal surgical specimens after neoadjuvant RCT.

2. Materials and methods

2.1. Patients

This study was approved by the institutional review board. Informed consent was obtained from all participants. A total of 124 patients, with mid/low rectal tumors, operated on between 2012 and 2014 in the Colorectal Surgery Department of Beaujon Hospital (Clichy, France), were prospectively included in the study. All patients had a biopsy confirming the diagnosis of rectal adenocarcinoma. All tumors were classified as locally advanced (T3-T4 and/or N+) by cross-sectional imaging (magnetic resonance imaging and/or transrectal ultrasonography). Mid and low rectal tumors were defined as localized between 7 and 12 cm and less than 7 cm from the anal verge, respectively. All patients underwent neoadjuvant RCT consisting of long-course radiotherapy (45-50 Gy over 5-6 weeks) and concomitant 5-fluorouracil–based chemotherapy. They were operated on by 2 experienced surgeons (Y. P. and L. M.), according to the principle of TME. Patients also received postoperatively 5-fluorouracil chemotherapy if they were staged as ypN+ or if they had distant metastasis.

2.2. Pathologic data

A prospective protocol for an extensive macroscopic and microscopic workup of the surgical specimens was determined by a gastrointestinal pathologist (N. G.).

All specimens had macroscopic examination before fixation in formalin. The quality of TME was evaluated according the principle of Nagtegaal et al [24].

The external surface of the specimen was painted with black ink. Rectal cancer specimens were longitudinally opened along the antimesenteric border sparing the tumor. Gross aspect of the tumor scar was described. We measured precisely the tumor and the distal resection margin. To maintain the original anatomy and to realize correctly the cross-sectional section of the tumor area, the section opened was sutured. After 48 hours of fixation in 4% formalin, the entire specimen was transversally cut in 5- to 10-mm-thick slices perpendicular to the longitudinal axis of the rectum from the distal resection margin up to the vascular pedicle. No fat-clearing techniques were used. The whole tumor area with its fatty tissue was sampled together to measure correctly the circumferential margin. Mesorectal fat below and above the tumor was manually thoroughly dissected, and each lymph node (LN) and/or mesorectal extranodal cancer tissue (EX) visualized or palpated were embedded. Our pathologic workup procedures, using standard cassettes, are schematized in Fig. 1. For mapping tumor-related LN and/or EX, different compartments were predefined (Fig. 2): below the lower edge of the tumor (A), peritumoral (B), above the upper edge of the tumor (C). Proximal compartment were subdivided into 3 groups: between 0 and 3 cm above the upper edge of the tumor (C1), peritonized mesorectum (C2), and vascular pedicle (C3).

Tissue samples were embedded in paraffin, and 4-μm sections were cut and stained with hematoxylin and eosin. Slides of all cases were prospectively viewed by the same pathologist (N. G.). Microscopic examination of the cancer specimen and tumor regression grade was performed according the "protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum" established by the College of American Pathologists and based on American Joint Committee on Cancer (AJCC)/Union for international Cancer Control (UICC) TNM 7th Edition [25].

Cancer spread in the mesorectum and the rectal wall were both examined. Modes of distal intramural spread included vascular and perineural invasion and tumor direct extension as described in previous studies [6,9]. Modes of mesorectal cancer spread included LN metastases (MLNs) and EX. LN was defined as at least partially encapsulated lymphoid aggregates irrespective of their size. Any recognizable residual tumor, whatever its size within a LN, was considered as metastatic. Then, LN with a micrometastasis, defined by the AJCC/UICC 7th Edition, was considered as MLN as