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Radiotherapy of rectal cancer in elderly patients: Real-world data assessment in a decade

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ABSTRACT

Background and purpose: There is paucity of data on the efficacy and toxicity of radiotherapy in rectal cancer (RC) elderly patients. The objective was to identify management strategies and resulting outcomes in RC patients ≥70 years undergoing radiotherapy.
Material and methods: A retrospective study included consecutive RC patients ≥70 years undergoing rectal radiotherapy.
Results: From 2004–2015, 340 RC patients underwent pre-operative (n = 238; 70%), post-operative (n = 41, 12%), or exclusive (n = 61, 18%) radiotherapy, with a median age of 78.5 years old (range: 70–96). Radiotherapy protocols were tailored, with 54 different radiotherapy programs (alteration of the total dose, and/or fractionation, and/or volume). Median follow-up was 27.1 months. Acute and late grade 3–4 radio-induced toxicities were reported in 3.5% and 0.9% of patients. Metastatic setting (OR = 6.60, CI95% 1.47–46.03, p = 0.02), exclusive radiotherapy (OR = 5.08, CI95% 1.48–18.21, p = 0.009), and intensity-modulated radiotherapy (OR = 6.42, CI95% 1.31–24.73, p = 0.01) were associated with grade ≥3 acute toxicities in univariate analysis. Exclusive radiotherapy (OR = 9.79, CI95% 2.49–43.18, p = 0.001) and intensity-modulated radiotherapy (OR = 12.62, CI95% 2.05–71.26, p = 0.003) were independent predictive factors of grade ≥3 acute toxicities in multivariate analysis. A complete pathological response was achieved in 12 out of 221 pre-operative patients (5.4%). Age, tumor stage, and surgery were independent predictive factors of survival in multivariate analysis. At end of follow-up, 7.1% of patients experienced local relapse.
Conclusion: Radiotherapy for RC in elderly patients appeared safe and manageable, perhaps due to the tailoring of radiotherapy protocols. Tailored management resulted in acceptable rate of local tumor control.

1. Introduction

Pre- or post-operative radiotherapy is a cornerstone of rectal cancer (RC) management. However, the recurrence pattern of RC has been significantly modified with the systematic use of Total Mesorectal Excision surgery (TME), decreasing the risk of local relapse to less than 15% [1–3]. Since high rates of local tumor control are already achieved with exclusive surgery, the therapeutic indexes (efficacy/toxicity ratios) of additional radiotherapy and chemotherapy should be carefully evaluated. This topic is certainly of major interest for elderly patients, since 70% of RC patients are above 70 years of age at diagnosis [4] and since elderlies were shown to often not undergo optimal (*i.e.* pre-operative and surgical) treatment [5]. The two main validated options for aged patients are either the pre-operative normo-fractionated protocol [6]: 50 Gy in 25 fractions concomitantly performed with a 5-FU-based chemotherapy, or the pre-operative hypo-fractionated protocol: 25 Gy in 5 fractions without chemotherapy [5]. But in

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daily-routine practice, chemotherapy and radiotherapy dose, fractionation and setting are often tailored with great care according to patient characteristics (age, comorbidity, frailties. . .), although guidelines for tailoring management are not currently available. In the absence of a consensus regarding treatments specifically adapted to the geriatric population, any therapeutic decision is complex [7]. Although data are now available to guide chemotherapy decision and/or choice in colorectal cancer [8], data are scarce concerning radiotherapy. Moreover, although oncogeriatric scales influence the final therapeutic decision, they do not define new target volumes, new radiation doses/fractionations, and adapted concurrent chemotherapy [9]. Therefore the therapeutic index of radiotherapy and chemotherapy is still to be determined in the heterogeneous population of elderly RC patients [10–12], with particular concerns regarding chemoradiation [13]. The objective of this study is to report the outcomes of real-life RC management in elderly patients.

2. Methods and materials

A retrospective study was conducted at the Lucien Neuwirth comprehensive cancer care center (Saint Priest en Jarez, France). The institutional review board approved the study, which was conducted in compliance with the Helsinki Declaration.

2.1. Patient population

Medical records of consecutive patients ≥70 years undergoing radiotherapy for a RC between 2004 and 2015 were retrospectively reviewed. Patient characteristics (age, sex, ECOG performance status, body mass index (BMI)), tumor histology and staging, radiotherapy characteristics (treated locations, dose, fractionation, setting), chemotherapy characteristics, resulting acute and late toxicities, complete sterilization of the operative specimen (ypCR), and complete (R0) tumor resection were also studied.

2.2. Treatment definition

2.2.1. Concomitant chemo-radiotherapy association

Tailored chemotherapy protocols and dose adaptations could be performed, depending on medical oncologist's choice. Chemoradiation was defined as concurrent when chemotherapy overlapped radiotherapy.

2.2.2. Radiation therapy

Patients were treated in supine position, and immobilized using leg-positioning foamed wedges. Computerized tomography (CT-scan) images were acquired without contrast agent infusion with a slice thickness of 2.5 mm. Plans were contoured and calculated using the Eclipse treatment planning system (Varian Medical Systems, Palto Alto, CA).

2.2.2.1. Volume definition. Gross tumor volume (GTV), clinical tumor volume (CTV), planning tumor volume (PTV) and organs at risk (OAR) were delineated on planning CT-scan. Their definition evolved with the availability and development of CT-scan, Magnetic Resonance Imaging (MRI), and with delineation guidelines editions. GTVs included the macroscopic tumor and its eventual anal or mesorectal extensions (GTV-T), and the macroscopically (on the diagnostic CT-scan or MRI) involved pelvic or mesorectal lymph nodes (GTV-N). The rectal boost (optional) was delivered on a PTV including the GTV T plus margin. The CTV included the GTV-T plus margin, the GTV-N plus margin, the mesorectum, internal iliac arteries, and the presacral lymph node area. PTVs were obtained adding a systematic margin to CTVs.

2.2.2.2. Dose prescription. Data on radiation prescription were collected, with total dose on pelvis, total dose on rectum, and fractionation. Firstly, radiation protocols were considered different if one of these parameters varied, considering doses and fractionation as continuous variables. Secondly, in order to statistically study the impact of radiation program adaptation on outcomes, protocols were grouped according to three parameters: total dose on pelvis, total dose on rectum (i.e. rectal boost or rectal dose escalation), and fractionation. As these parameters were then considered as binary variable (ex: decrease total dose *vs.* normal total dose), 8 different protocols could be compared using logistic regressions. Hypofractionation was defined by a dose of ≥2.5 Gy per fraction. Equivalent 2 Gy (EQD2) dose was calculated using the EQD2 formula provided by Fowler [14] and $\alpha/\beta = 6.2$ [15].

2.3. Evaluation of efficacy, acute and late toxicities

Follow-up was calculated from the completion of radiotherapy. As recommendations suggest to perform the rectal surgery 6–8 weeks after pre-operative radiation completion, the impact of a "late" surgery was studied through the "56 days" cut off (*i.e.* the end of the 8th week): patients experiencing surgery more than 56 days after radiation completion were considered to experience "late" surgery.

Patients were assessed for toxicity every week during radiation course, and every 3 months later. Radiation-related toxicities were retrospectively graded using the Common Terminology Criteria for Adverse Events v4.0 (CTCAEv4.0) [16]. Acute toxicity was defined by a toxicity occurrence within 3 months from the beginning of radiotherapy. Late toxicity was defined by a toxicity occurrence on top of the 3 months following the beginning of radiotherapy, and could also be reported by surgeons and/or general practitioners. Chemotherapy-induced toxicities were collected in medical oncology files. After radiotherapy completion, patients were assessed for efficacy every 3 months by surgeons and medical oncologists during the first two years and every 6 months later, with clinical examination and alternation of chest/abdomen/pelvis-CT-scan and chest radiography and abdominal ultrasound.

2.4. Statistical analysis

Progression-free survival (PFS) was defined as the time from the date of radiotherapy completion to the date of clinical and/or radiological RC progression. Disease-free survival (DFS) was defined as the time from the date of tumor resection to the date of clinical and/or radiological progression. Overall survival (OS) was defined as the time from the date of radiotherapy completion to the date of death or the last follow-up. Specific survival (SS) was defined as the time from the date of radiotherapy completion to the date of a death caused by the RC. Medical files of oncology, radiotherapy, surgery and of patient's general practitioners were systematically reviewed to identify the death cause. In case of doubt, a panel of three authors assigned the death cause in the light of the available information. PFS, DFS, SS and OS were estimated with the Kaplan–Meier method. Comparisons of median survival were performed using a Log-rank test. Median values were given with the interquartile range (IQR) or with the range (min–max). Chi-2 test or Fisher test were performed to compare patient characteristics distribution. A Cox proportional hazards model was used to test the interaction between data on survival or on local control and treatment or patient characteristics. All p values were nominal without adjustment for multiple testing. Significance was defined by $p < 0.05$. The multivariate analysis was performed using a Cox multivariate analysis based on the significant -or close-to-significance ($p < 0.20$)- factors. A variable selection procedure (stepwise Akaike information criterion (AIC)) based on the Akaike criterion was then used to produce the best

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