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ORIGINAL ARTICLE

Hemostatic radiotherapy for bladder cancer-related hematuria in patients unfit for surgery: is there any impact of fractionation schedule?

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Summary

Purpose: *The optimal schedule for palliative external beam radiotherapy (EBRT) in patients with bladder tumors with hematuria unfit for surgery remains undefined. This study aimed to assess the clinical hemostatic efficacy and safety of two EBRT hypofractionated schedules.*

Methods: *From February 2008 to October 2017, 31 patients were referred to our department for palliative hemostatic bladder irradiation. EBRT consisted of two schedules: "continuous" treatment (CRT) was delivered following consecutive 3-10 weekdays (3-6Gy/fraction (fr), to a total dose of 18-30Gy) (n=14); the "discontinuous" schedule (DRT) consisted of 23Gy in 4fr (6.5Gy/fr on days 1 and 3, followed by 5Gy/fr on days 15 and 17; n=12). The primary endpoint was the rate of hemostatic control (HC) at the end of the radiation course. Other endpoints included mid-term HC, toxicities and overall survival. Comparative analyses were performed by exact Fisher test with a cut-off of 0.05 for statistical significance.*

Results: *The rate of HC at the end of EBRT was 92% (n=24) with no differences between CRT and DRT (100% vs 86%; p=0.48). The median follow-up was 6 months, HC was achieved in 15/26 (58%) patients at the last follow-up, without meaningful differences between CRT and DRT (50% vs 67%; p=0.45). Three and two patients developed acute grade ≤2 diarrhea in CRT and DRT groups, respectively.*

Conclusion: *Our study suggests that both hypofractionated "continuous" and "discontinuous" EBRT are well tolerated and represent acceptable schedules for patients with limited life expectancy. DRT schedule could be preferred for departments' organization to increase the slots for the treatment of other referred patients for radiotherapy.*

Key words: *cancer; hematuria; palliative care; radiotherapy*

Introduction

Cancer-related hematuria is a typical manifestation of bladder cancer (BLC), although it may also occur in other malignancies and is associated with significant morbidity and mortality. External beam radiotherapy (EBRT) is a non-invasive and efficient treatment modality, although based on a very limited literature consisting mainly of small retrospective series [1-6] in patients not eligible for curative treatment. In fact, most palliative EBRT studies addressed several endpoints, including hemostatic control (HC), and few studies used specifically HC as their primary endpoint [6-9].

The optimal radiotherapy schedule remains to be defined: various hypofractionated radiotherapy

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(HFRT) schemes derived from retrospective series have been proposed, namely 30Gy in 10 fractions (fr), 20Gy in 5fr, and 23Gy in 4fr. All these protocols have shown heterogeneous efficacy results in terms of HC.

The aim of this study was to assess short and mid-term clinical hemostatic efficacy and safety of two different EBRT hypofractionated schedules for patients with gross hematuria due to bladder tumor invasion who were not candidates for curative treatment (surgery or chemoradiation).

Methods

Patients

From February 2008 to October 2017, the charts of 31 consecutive patients referred to our department for palliative hemostatic EBRT were reviewed. Patients who were eligible for curative intent therapy were excluded. Twenty-six of the 31 patients were eligible for efficacy and safety analyses. Four patients were not evaluable because they were either lost to follow-up immediately after treatment or referred to another center. One additional patient was excluded from the analysis because he received a scheme not suitable for this study (8Gy in a single fraction). Median age was 78.8 years with a clear predominance of males (n=22; 84%). All patients presented gross hematuria related to bladder invasion (n=22) or prostate cancer (n=4). Median Eastern Cooperative Oncology Group (ECOG) performance status was 2, and 7 patients presented with metastatic disease. Most patients had undergone a surgical procedure before being referred to our department, consisting of transurethral bladder resection (n=18) or prostatectomy (n=3). Eight patients required iterative blood transfusions. Baseline hemoglobin level was assessed in all patients. Patients' characteristics are summarized in Table 1.

EBRT modality

EBRT consisted of two schedules: "continuous" or "discontinuous". Continuous treatment (CRT) was delivered following consecutive 3-10 weekdays. The different schemes used were: 30Gy in 10 fr, 20Gy in 5 fr, and 18Gy in 3 fr.

The discontinuous schedule (DRT) consisted of 23Gy in 4fr delivered in two phases: induction treatment (6.5Gy on days 1 and 3), followed by a consolidation treatment (5Gy on days 15 and 17) (Figure 1). Alternatively, patients could receive 5Gy on days 1 and 3 followed by 6.5Gy on days 15 and 17. DRT patients were reassessed clinically on day 15 before validation of the second phase, depending on general condition and resolution of the bleeding. Unless a significant deterioration of the general condition was noted, consolidation was offered. The distribution of patients according to EBRT schedules is presented in Table 2.

In both CRT and DRT, the clinical target volumes (CTV) encompassed the whole bladder, with expansion of 1-1.5 cm for planning target volume (PTV). Elective regional lymph nodes were not considered. Expansion for PTV was isotropic or anisotropic with larger craniocaudal expansion. HC and toxicities were assessed 7-15 days after irradiation and at each subsequent follow-up visit.

Objective assessment and statistics

The primary endpoint was the rate of HC at the end of the radiation course and at the last follow-up. HC corresponded to the resolution of gross hematuria. Secondary endpoints were toxicities and overall survival. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (10). Comparative analyses were performed by the exact Fisher test with a cut-off of 0.05 for statistical significance. Overall survival (OS) was defined as the time interval from diagnosis to death (from all causes) or last follow-up. OS was computed using the Kaplan-Meier method and log-rank test. The statistical analyses were performed with the R software version 3.4.3 (R-project, Vienna, Austria).

Table 1. Population description

Characteristics	*Number of patients*
Total population	31
Evaluable population:	26
Age, years	77.7 (38-99)
ECOG PS	1.96 (0-4)
Primary Bladder	22
Primary Prostate	4
Metastatic disease	7
Surgery before RT	21
Hemoglobin	8,7 g/gL (3.5-12.7)
Transfusions before RT	
0	18
1-2	2
>2	6

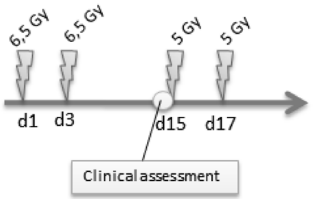

Figure 1. Discontinuous EBRT schedule.

Table 2. EBRT schedules

EBRT schedules	*No. of patients*
Continuous schedules	14
30 Gy in 10 fr	3
20 Gy in 5 fr	10
18 Gy in 3 fr	1
Discontinuous schedules	
23 Gy in 4 fr	12

Table 3. Studies investigating EBRT for bladder related bleeding (follow-up)

Authors	*No. of patients*	*Total*	*No. of fractions*	*Daily dose*	*Hemostatic control (%)*
Srinivasan, 1994 [1]	22	17 Gy	2	8.5 Gy	59
	19	45 Gy	12	3.75 Gy	16
McLaren, 1997* [9]	37	30/36	5/6	6 Gy	92
Jose, 1999* [8]	14	30/36	5/6	6 Gy	50
Rasool, 2011** [2]	15	15 Gy	5	3 Gy	91
	10	20 Gy	5	4 Gy	
Lacarriere, 2013 [4]	13	30 Gy	10	3 Gy	54
	19	20 Gy	5	4 Gy	79
Kouloulias, 2013* [7]	50	36 Gy	6	6 Gy	94
Alijabab, 2014*** [14]	74	4-30 Gy	1-10	3-10 Gy	73
Dirix, 2016* [6]	38	34.5 Gy	6	5.75 Gy	89
Coraggio, 2018	14	18-30 Gy	3-10	3-6 Gy	100
	12	23 Gy	4	5-6.5 Gy	86

*These studies focused on general symptoms palliation. Here are reported only the data concerning patients with macroscopic hematuria before radiotherapy.
**This study included patients with bleeding from different cancers, but the Hemostatic Control percentage refers only to the 12 patients with hematuria.
*** Abstract only.

Results

The rate of short term HC at the end of EBRT was 92% (n=24) with no significant differences between CRT (100%) and DRT (86%; p=0.48). With a median follow-up of 6 months, mid-term HC was achieved in 15/26 (58%) patients, without meaningful differences between CRT (50%) and DRT (67%; p=0.45). When excluding the three patients who received 30Gy in 10 fr from the analysis, there was no significant difference in HC at the end of EBRT (100% vs 86%) and at last follow up (70% vs 67%) between the CRT and DRT groups, respectively. One patient who received 20Gy in 5 fr (CRT), despite achieving HC after EBRT, was re-irradiated 10 months after for new macroscopic hematuria with the same schedule (20Gy in 5fr) without achieving HC. Two patients who were treated with DRT achieved initial HC but presented recurrent hematuria at 6 and 11 months, respectively. They were both re-irradiated with a dose of 10Gy in two non-consecutive fr, obtaining HC in one. Three of 12 patients from the DRT group achieved complete short and mid-term HC at the end of the first part of the EBRT sequence, thus receiving a total dose of only 13Gy in 2 fr. Three and two patients developed acute grade <2 diarrhea in the CRT and DRT groups, respectively. The median survival was 6 months in the whole population. Three (11%) patients were still alive at two years

Discussion

Various retrospective studies have reported the efficacy of different radiotherapy schedules to palliate bladder invasion-related symptoms, including pain, dysuria, etc. However, only a few addressed the role of EBRT to achieve HC (Table 3). Even though the studies were very heterogeneous in term of doses and techniques, all consistently showed a high rate of HC with low toxicity rates.

In their randomized prospective trial, Duchesne et al compared two radiation schedules (35Gy in 10fr versus 21Gy in 3fr) for symptomatic improvement in patients with bladder cancer deemed unfit for curative intent therapy. Among the 272 patients, overall response (defined as improvement of at least one symptom by one grade without worsening of any other) was achieved in 71% in the 35Gy arm and 64% in the 21Gy arm with no statistical difference (p=0.19). Importantly, this trial, that involved old radiation techniques, was not intended to assess HC with EBRT, therefore reported data concerning only overall response [3]. Lacarrière et al compared retrospectively the 30Gy in 10fr schedule for patients with ECOG PS 0-2 (13 patients) with the 20Gy in 5fr schedule for patients with ECOG PS >2 (19 patients) and found no significant difference in terms of HC [4].

The two schedules, "continuous" and "discontinuous", of hypofractionated EBRT that we com-

pared were well tolerated and achieved excellent short-term HC without any difference between the two groups. However, the discontinuous scheme allows using fewer numbers of sessions, thus involves less travelling and is less burdensome for frail patients. From the perspective of the radiotherapy department, it allows reducing the waiting time for treatment and the working load on the machines. Finally, the cost-effectiveness is important for society in the context of the upward trend in health care. Despite most cost-effectiveness analysis in the palliative context comparing single fraction to multiple fractions [11], we can translate this benefit to DRT (4fr) vs CRT (5-10fr), with due proportions.

It is unclear whether the consolidation phase of EBRT should be given to all fit patients or only to those who did not experience HC, keeping in mind the possibility of second or even third courses of irradiation, if necessary, according to the patient's overall condition.

Although short-term HC with EBRT was satisfactory in our series, the lower results at mid-term indicate that the dose delivered in the palliative setting is unlikely to be curative. For comparison, the schedules used in Phase III studies investigating chemoradiation for bladder cancer were 55Gy in 20fr and 64Gy in 32fr [12].

In the context of palliative bony metastases, there is level I evidence showing equivalence of several radiation schedules (30Gy in 10fr, 20Gy in 5fr and 8Gy in a single fr) in terms of pain control [11,13]. For palliative hemostatic EBRT, the data are limited in the literature, consisting mainly of small retrospective series.

This study has some limitations. First, it is a retrospective study and, as a consequence, the population of the study was heterogeneous in terms of tumor staging, performance status, previous treatment received and radiation dose schedules. Second, the sample size was small. Moreover, our study included not only primary tumors but also secondary tumors. The short follow-up was related to the poor prognosis of this population.

Conclusion

Our study suggested that "continuous" and "discontinuous" radiotherapy schedules are equally effective in achieving short-term HC in patients with cancer-related macroscopic hematuria with a low toxicity profile. "Discontinuous" EBRT schedule seems to be more appropriate for frail patients with mobility impairments, reducing the number and frequency of displacements. Furthermore, radiotherapy departments with few accelerators may use the increased slots to treat other patients and this advantage may be even greater when patients obtain HC with only the first part of EBRT sequence (2 fractions). Prospective studies are warranted to confirm our results.

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Conflict of interests

The authors declare no conflict of interests.

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