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La radiologia medica
Official Journal of the Italian Society of Medical Radiology

ISSN 0033-8362

Radiol med
DOI 10.1007/s11547-013-0346-z

Springer

Radiol med
DOI 10.1007/s11547-013-0346-z

RADIOTHERAPY

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Received: 20 September 2012 / Accepted: 30 January 2013

Abstract
Objective This study was done to assess the impact of clinical factors and in particular the use of drugs for concomitant illnesses on late radiation-induced rectal bleeding in patients with prostate cancer.
Materials and methods Patients with histologically proven prostate adenocarcinoma treated with radical radiotherapy and followed up for at least 6 months were selected. The correlation between late rectal bleeding and a number of factors was investigated by univariate and multivariate analysis.
Results A total of 278 patients who underwent radiotherapy at our institution between October 2002 and May 2011 were selected. At univariate analysis, delivery of radiation doses higher than 70 Gy and use of angiotensin-converting enzyme inhibitors were associated with a higher incidence of rectal bleeding. Conversely, patients who used calcium channel blockers had a lower risk (3-year rectal bleeding-free survival 89.8 versus 66.5 %, $p = 0.043$). At multivariate analysis, use of calcium channel blockers was found to have a protective effect with a hazard ratio of 0.3 (95 % CI 0.12–0.96). Delivery of higher radiation doses was associated with an increased risk of rectal bleeding (hazard ratio 3.02, 95 % CI 1.23–7.38).
Conclusions Use of calcium channel blockers during and after radiotherapy treatment might have a protective effect against late rectal bleeding. If these results are reconfirmed by larger clinical series, calcium channel blockers may be tested as radioprotector agents in clinical trials.

Keywords Radiotherapy · Rectal bleeding · Radioprotector · Hypertension · Calcium channel blockers

Introduction

Prostate cancer is the most frequently diagnosed cancer in men [1]. Currently radiotherapy is the standard of care for high risk prostate cancer, while it is an option for low and intermediate risk disease [2]. Nevertheless, it is likely that the role of modern dose-escalated radiotherapy will further increase even in low and intermediate risk prostate cancer, since recent data suggest it could provide better biochemical disease-free survival than surgery in all risk classes [3].

Gastrointestinal and bladder complications represent the main limit to radiation dose escalation in prostate cancer. Particularly rectal bleeding is the most commonly reported bowel toxicity, with a cumulative incidence of up to 50 % in 5 years in patients undergoing three-dimensional (3D) dose-escalated radiotherapy [4].

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Published online: 06 December 2013

In recent years, several results have demonstrated a clear correlation between rectal dose-volume histograms and the risk of rectal bleeding [5, 6]. In order to spare as much volume of rectum as possible while delivering higher radiation dose to the prostate, more advanced and often more expensive techniques, such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have been introduced in clinical practice, leading to a reduction in the risk of rectal bleeding [7].

Besides dosimetric factors, also clinical variables such as previous abdominal surgery, presence of haemorrhoids, and use of antihypertensive medications can affect the risk of late rectal toxicity after radiotherapy [8]. Although arterial hypertension or the use of antihypertensive drugs seems to be protective for the development of late effects [8, 9], no clear effect has been shown for any specific antihypertensive drug.

The objective of this analysis was to assess the impact of clinical factors and in particular the use of drugs for arterial hypertension on late radiation-induced rectal bleeding. The effects of several potentially confounding parameters (comorbidity, abdominal surgery, radiotherapy dose and technique) were also analysed.

Materials and methods

Study design

Patients with histologically proven prostate adenocarcinoma treated with either 3D conformal radiotherapy (3DCRT) or IMRT for radical intent and followed up for a minimum of 6 months were selected for this retrospective analysis. Daily portal image verification was used in all patients for set-up correction [10]. To this end, if no previous prostatectomy had been performed, patients had intra-prostatic gold fiducials implanted. Comorbidities, previous abdominal/pelvic surgery, use and type of drugs, previous/concomitant locoregional diseases, height and weight, were recorded before radiotherapy. Information on quality and duration of hormone therapy, when prescribed, was also recorded. Patients were examined before starting treatment, weekly during radiotherapy, at the end of the radiotherapy course, 1 month after radiotherapy, and every 6 months thereafter. During follow-up visits, all patients were specifically asked whether they had noticed the presence of blood in their stool. Rectal toxicity occurring during and within 3 months after the end of radiotherapy, was also recorded according to Radiation Therapy Oncology Group (RTOG) criteria [11].

Statistical analysis

The correlation between late rectal bleeding and a number of factors was investigated by univariate and multivariate analysis. The following parameters were considered: body mass index ($>$ or $\leq$30), pre-treatment morbidities (arterial hypertension, diabetes mellitus, chronic pulmonary disease), hormone therapy, drug prescription during radiotherapy (use and type of antihypertensives and/or anticoagulants), abdominal surgery prior to radiotherapy (radical prostatectomy or other surgical procedures including rectum-sigma resection, kidney resection, cholecystectomy, appendectomy, prostatic adenomectomy), irradiation of pelvic nodes, delivered dose (equivalent dose in 2 Gy per fraction with $\alpha/\beta = 3$, EQD2 $>$ or $\leq$70 Gy), and technique used (IMRT or 3DCRT).

Standard time-to-event (survival analysis) methodology was used to assess the first reported incidence of toxicity. Events were timed from the end of radiotherapy, and the differences between the treatment groups were first tested using the log-rank test. After that a multivariate analysis was performed including all covariates that appeared to be associated with the endpoint in the first analysis (covariates with $p \leq 0.25$). Relative risks of late rectal bleeding according to treatment are summarised using hazard ratios (HR) with 95 % confidence intervals (CI) from Cox regression models.

The difference of the incidence of grade $\geq$2 acute rectal toxicity between the treatment groups was assessed using the Chi-square test with Yates correction.

Results

A total of 278 patients who underwent radiotherapy at our institution between October 2002 and May 2011 were selected for this analysis. The patient's characteristics are described in Table 1.

All patients treated with 3DCRT received a conventional 1.8–2 Gy fractionation regimen. Conversely, 98/161 (60.8 %) patients treated with IMRT received a moderate hypofractionated radiotherapy schedule (mean dose per fraction, 2.53 Gy; range 2.27–2.6 Gy). Mean delivered EQD2 was significantly lower in patients receiving 3DCRT (69.7 versus 72.5 Gy, $p < 0.001$). Mean delivered EQD2 was also lower in patients who received pelvic irradiation (70.2 versus 74.4 Gy, $p < 0.001$).

The prevalence of diabetes, hypertension, chronic pulmonary disease, and use of medications are described in Table 2.

Median follow-up time was 36 months (range 6–106); 65/278 (23.3 %) patients presented with rectal bleeding during follow-up.

Table 1 Patients' characteristics

	Mean	Range	
Age (years)	68	46–81	
	≤30	>30	Missing data
Body mass index, *n* (%)	178 (64.0)	64 (23.0)	36 (12.9)
Previous abdominal surgery, *n* (%)			
No	145 (52.1)		
Radical prostatectomy	92 (33.0)		
Other	41 (14.7)		
Treatment			
EQD2 (Gy)	71.5	59.8–80	
Radiotherapy technique, *n* (%)	3DCRT	IMRT	
	117 (42.0)	161 (58.0)	
Pelvic irradiation, *n* (%)	Yes	No	
	190 (68.3)	88 (31.6)	
Hormonal therapy, *n* (%)	Yes	No	
	250 (89.9)	28 (10.1)	

Table 2 Concomitant illnesses and medications

	Yes	No	Missing data
Concomitant illnesses, *n* (%)			
Diabetes	36 (12.9)	242 (83.1)	0
Arterial hypertension	137 (49.3)	141 (50.7)	0
Chronic pulmonary disease	17 (6.1)	261 (93.8)	0
Medications for cardiovascular comorbidities, *n* (%)			
Anticoagulants/antiplatelet drugs	64 (23.0)	197 (70.8)	17 (6.1)
Angiotensin-converting enzyme inhibitors	55 (19.7)	204 (73.3)	19 (6.8)
Angiotensin II receptor antagonists	37 (13.3)	222 (79.8)	19 (6.8)
Calcium channel blockers	43 (15.4)	217 (78.0)	18 (6.4)
Beta blockers	40 (14.3)	219 (78.7)	19 (6.8)
Alpha-blockers	45 (16.1)	216 (77.6)	17 (6.1)
Diuretics	43 (15.4)	216 (77.6)	19 (6.8)
Statins	33 (11.8)	227 (81.6)	18 (6.4)

At univariate analysis (Table 3) both delivery of EQD2 dose higher than 70 Gy and the use of ACE inhibitors were associated with an increased incidence of rectal bleeding. Conversely, patients who used calcium channel blockers or underwent pelvic irradiation had a lower risk.

A summary of the main results of multivariate analysis for the study endpoints is shown in Table 4.

While arterial hypertension had no effect on the risk of rectal bleeding, the use of calcium channel blockers showed a protective effect. IMRT use also seemed to have a protective effect against late rectal bleeding, although statistical significance was not reached. When IMRT was

Table 3 Univariate analysis of potential predictors for late rectal bleeding

Variables	Patients (*n*)	3-year rectal bleeding-free survival	*p*
Body mass index > 30			
Yes	64	77.5	0.24
No	178	69.9	
Previous abdominal surgery			
Yes	133	75.3	0.22
No	145	64.5	
IMRT use			
Yes	161	73.6	0.15
No	117	66.9	
EQD2 > 70 Gy			
Yes	195	66.6	**0.04**
No	83	78.8	
Pelvic irradiation			
Yes	190	76.4	0.05
No	88	58.4	
Hormonal therapy			
Yes	28	69	0.45
No	250	77.7	
Diabetes			
Yes	36	72	0.62
No	242	57.2	
Arterial hypertension			
Yes	137	66.2	0.56
No	141	73.2	
Pulmonary disease			
Yes	17	70.9	0.2
No	261	56.4	
Anticoagulants/antiplatelet drugs use			
Yes	64	78.2	0.3
No	197	68.6	
Angiotensin-converting enzyme inhibitors use			
Yes	55	56.1	**0.03**
No	204	73.8	
Angiotensin II receptor antagonists use			
Yes	37	65.9	0.72
No	222	71.3	
Calcium channel blockers use			
Yes	43	89.8	**0.04**
No	217	66.5	
Beta blockers use			
Yes	40	42.4	0.23
No	219	73.5	
Alpha-blockers use			
Yes	45	72.1	0.77
No	216	70.4	
Diuretics			
Yes	43	58.7	0.51

Table 3 continued

Variables	Patients (*n*)	3-year rectal bleeding-free survival	*p*
No	216	73.1	
Statins			
Yes	33	75.8	0.34
No	227	69.8	

Bold values are statistically significant at $p < 0.05$

Table 4 Multivariate analysis of potential predictors for late rectal bleeding

Variables	Hazard ratio	0.95	CI	*p* value
Body mass index > 30	0.50	0.23	1.10	0.08
Chronic pulmonary disease	2.77	0.93	8.20	0.06
Angiotensin-converting enzyme inhibitors use	1.47	0.78	2.78	0.23
Beta blockers use	1.30	0.59	2.83	0.51
Calcium channel blockers use	0.34	0.12	0.96	**0.04**
EQD2 > 70 Gy	3.02	1.23	7.38	**0.01**
Pelvic irradiation	0.66	0.34	1.27	0.21
IMRT use	0.57	0.30	1.11	0.10
Previous abdominal surgery	1.19	0.60	2.36	0.60

Bold values are statistically significant at $p < 0.05$

used, 3-year rectal bleeding-free survival was 94.4 and 67.0 % with and without calcium channel blockers, respectively ($p = 0.038$).

Delivery of higher radiation doses was associated with increased risk of rectal bleeding. Even the presence of chronic pulmonary disease seemed to favour the development late rectal bleeding, although statistical significance was not reached.

Biochemical disease-free survival was not affected by calcium blockers use or radiation dose.

Discussion

In recent years many attempts have been made to protect the rectum against radiation damage by using topical or oral medications [12–15]. Both misoprostol rectal suppositories [13], and amifostine enemas [14] seem to exert some protective effect on late proctitis, while oral balsalazide appears to be effective in reducing the symptoms of acute proctitis [12]. Conversely, topical sucralfate appears to have no appreciable effects on acute and late proctitis [15]. In this analysis, we found that the use of calcium channel blockers for arterial hypertension during and after radiotherapy may exert some protective effect against the development of rectal toxicity. Although many authors have reported that arterial hypertension or antihypertensive medications may be protective for the development of late radiation-induced rectal effects [8, 9], this is the first time a protective effect was shown for a specific antihypertensive drug.

The potential use of calcium antagonists as radioprotectors was suggested by Battaini et al. [16] because of the imbalance in calcium homeostasis produced by radiation injury. Furthermore calcium channel blockers have antioxidant properties and have been shown to protect against free radical-mediated injury of cardiovascular cells [17] suggesting a possible mechanism for radioprotection.

Until recently, it was considered that the initial damage of the intestinal toxicity of irradiation was the destruction of epithelial stem cells within the crypts of Lieberkühn, causing the destruction and progressive failure of cell renewal, which explains the time delay between rectal mucosa irradiation and the onset of symptoms [18, 19]. More recently it has been suggested that an endothelial injury may occur before crypt stem cell damage in the evolution of the radiation-induced gastrointestinal syndrome [20]. Nifedipine, a calcium channel blocker, has been shown to improve endothelial function in patients with hypertension, at least partly, by enhancing endothelial progenitor cell numbers and activity, thus preserving endothelial integrity [21, 22].

In addition, calcium channel blockers are well tolerated and associated with minimal side effects [23], the most common being flushing, headache, hypotension, and pedal oedema. Adverse effects have been reported in approximately 17 % of patients using nifedipine, in 9 % of patients using verapamil, and in 4 % of those using diltiazem [24].

Although with the limits of a retrospective analysis, in our experience the use of calcium channel blockers resulted in a protective effect against late rectal bleeding.

A recent systematic review of 11 published reports including 4,559 patients suggests there is at a minimum no difference, and in many cases superiority, for IMRT compared with 3DCRT for the radical treatment of localised prostate cancer in terms of acute and late gastrointestinal and genitourinary side effects in the setting of dose-escalated (>70 Gy/2 Gy fractions) radiotherapy [25]. In our experience, IMRT use seems to reduce the risk of late rectal bleeding (HR 0.57), even though statistical significance was not reached at multivariate analysis ($p = 0.10$).

Since the burden of cancer is growing, and the disease is a major economic expenditure for all developed countries [26], low-cost strategies to improve radiation therapy tolerance appear very attractive. The use of calcium channel blockers seems to be effective in reducing the incidence of late rectal bleeding after prostate cancer radiotherapy, even when IMRT is employed.

If these results are confirmed in larger clinical series, calcium channel blockers may be tested as radioprotector agents in clinical trials.

Acknowledgments The authors thank Milly Buwenge for her contribution in revising the English language of this manuscript.

Conflict of interest Mariangela Massaccesi, Edy Ippolito, Francesco Deodato, Savino Cilla, Cinzia Digesù, Gabriella Macchia, Luciana Caravatta, Vincenzo Picardi, Gian Carlo Mattiucci, Alessandra Di Lallo, Daniele Cuscunà, Numa Cellini, Vincenzo Valentin, Alessio G. Morganti declare no conflict of interest.

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