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Late toxicity following conventional radiotherapy for prostate cancer: analysis of the EORTC trial 22863

Fatma Ataman [a,*], Alfredo Zurlo [a], Xavier Artignan [b], Geertjan van Tienhoven [c], Leo E. Blank [c], Padraig Warde [d], Jean B. Dubois [e], Wendy Jeanneret [f], Frans Keuppens [g], Jacques Bernier [h], Abraham Kuten [i], Laurence Collette [a], Marianne Pierart [a], Michel Bolla [b]

[a] *EORTC Data Center, Radiotherpy Group, Avenue E. Mounier 83, bte 11, B – 1200 Brussels, Belgium*
[b] *Department of Radiotherapy, CHU de Grenoble – La Tronche, Bp 217 X, F – 38043 Grenoble Cedex, France*
[c] *Academisch Medisch Centrum, Department of Radiotherapy, Meibergdreef 9, NL-1105 AZ Amsterdam, The Netherlands*
[d] *Department of Radiation Oncology, University Health Network – OCI/Princess Margaret Hospital, 610 University Avenue, Toronto, Ont., Canada M5G 2M9*
[e] *Department of Radiotherapy, CRLC Val D'aurelle, Pare Euro Medicine – Rue de la Croix Verte, F – 34298 Montpellier Cedex 5, France*
[f] *Department of Radiotherapy, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland*
[g] *Department of Urology, Akademisch Ziekenhuis VUB, Laarbeeklaan 101, B-1090 Brussels, Belgium*
[h] *Department of Radiation Oncology, Ospedale San Giovanni, Rue de l'Hopital, CH-6500 Bellinzona, Switzerland*
[i] *Rambam Medical Center, Department of Oncology, Bat Galim – P.O. Box 9602, IL-31096 Haifa, Israel*

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Abstract

Late toxicity and other serious adverse events (SAE) were analysed in the European Organisation for Research and Treatment of Cancer (EORTC) trial 22863. The study evaluated the value of adjuvant endocrine treatment for locally advanced prostate cancer treated with radiotherapy. From 1987 to 1995, 415 patients were randomised. There was long-term toxicity information for 377 patients (91%). Median age was 70 years (range 50–80 years). Median follow-up for late toxicity was 42 months (range 3–136 months). Toxicity was graded according to a modified Radiotherapy and Oncology Group (RTOG) scale. Other late SAE, that was not classified as severe treatment toxicity, but were still life-threatening, were also assessed. There were 72 patients with grade 2, 10 patients with grade 3 and 4 patients with grade 4 toxicity. There were 20 patients with other late SAE, who were grouped according to their relationship to treatment; likely related ($n = 1$), unrelated ($n = 7$) and not assessable($n = 12$). Although four treatment-related deaths (1%) occurred, grade 3 or 4 late complications were less than 5%.

Keywords: Prostate cancer; Radiotherapy; Late toxicity; Serious adverse events

1. Introduction

Locally advanced prostate cancer patients are currently offered a number of therapeutic options, ranging from conventional and three-dimensional conformal radiation therapy (3D-CRT) to surgery and hormonal therapy, either as a sole treatment modality or in combination with radiotherapy or surgery. Although adjuvant hormonal treatment can increase overall survival or progression-free survival, all of these different modalities are considered as a therapeutic option for locally advanced prostate cancer [1–7]. Therefore, the risk of chronic and debilitating morbidity associated with each of the therapeutic strategies is particularly important in the decision-making process and should be brought to the patients' attention.

Acute side-effects of radiation occur during or shortly after completion of treatment. Acute toxicity is generally minor to moderate in severity and rarely

* Corresponding author. Tel.: +32-2-774-1611; fax: +32-2-772-3545.
E-mail address: fat@eortc.be (F. Ataman).

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results in permanent toxicity or disability, as opposed to late toxicity that manifests itself several months to several years after treatment completion. Late effects are dose-limiting, since they can be permanent and progressive. Definitions and classifications of late toxicity vary in the prostate cancer studies that have been reported, due to the different scoring systems that have been used [8–10]. Regardless of the scoring system employed, physicians try to anticipate the occurrence of severe toxicity, and agree to assess and compare different treatment modalities based on their therapeutic ratios. For clinical trials, it has recently become mandatory to report to the regulatory agencies the occurrence of any serious medical events with a possible causal relationship to the drug under study. This extensive reporting system aims to gather a wealth of information in order to identify all of the adverse consequences of a treatment modality potentialy linked to a particular therapy.

In this paper, we report the type and frequency of significant late toxicities, as well as other late serious adverse events (SAE) observed in a series of patients with locally advanced prostate cancer who were treated with conventional radiation in the framework of a large, multi-centre, prospective, randomised clinical trial. Other SAE included the events that were not regarded as treatment toxicity, but could still threaten the patient's life. Analysis of survival [1–3], health economics [11], quality assurance [12] and acute toxicity [13] have already been published elsewhere.

2. Patients and methods

2.1. Trial

The European Organisation for Research and Treatment of Cancer (EORTC) phase III trial 22863 compared conventional external beam irradiation with conventional external beam irradiation (RT) plus 3-years gonadotropin-releasing hormone agonist administration in patients with locally advanced prostate cancer stage T3-4 any G or T1-2 G3 NOMO. Different groups (i.e., Genitourinary Tract and Radiotherapy) from 26 centres entered patients into this trial. Survival data showed a significant advantage in favour of the combined treatment [2], and this was recently confirmed in an updated long-term analysis [3]. A specific quality assurance programme was implemented to evaluate the protocol compliance among the participating centres [12]. Assuming that the duration of the combined hormonal treatment has little or no effect on radiation-induced toxicity, this trial provides a series of homogeneously irradiated patients from 1987 to 1995.

2.2. Patients and treatment

Four hundred fifteen patients were randomised and 405 completed the radiotherapy (RT) treatment. Details of the RT technique and dose specification have been described previously in [3]. Briefly, the study protocol recommended whole-field pelvic irradiation (planning target volume (PTV I)) up to a dose of 50 Gy using conventional fractionation followed by a 20-Gy prostatic boost (PTV II) to deliver a total dose of 70 Gy. A four-field box isocentric technique for the whole pelvis (large field) and the same technique or a three-field coplanar technique was recommended for the boost using $\geqslant$10 MV photons. Some centres employed limited field irradiation (small field) to the prostatic area with a four-field box technique to a total dose of 70 Gy. A few centres delivered radiation by Co60.

Three hundred seventy seven patients (91%) were assessable for late toxicity, while the rest (9%) either did not complete RT or did not have follow-up information for late toxicity evaluation. Median age of the 377 cases was 70 years (50–80 years) and median follow-up for toxicity was 42 months (3–136 months). Patient characteristics are presented in Table 1. Of the 377 patients, most (89%) received a total dose between 68 and 70 Gy, 1% received >70 Gy, 8% received 60–67 Gy, and 2% <60 Gy. A total of 65 patients (17%) received limited field irradiation to the prostatic area. Patients were irradiated

Table 1
Characteristics of the 377 patients assessable for toxicity

Patient characteristics	Number of cases
Age (years)	
>70	202
$\leqslant$ 70	175
Treatment arm	
Arm 1 (no hormonal treatment)	189
Arm 2 (hormonal treatment)	188
Total radiation dose	
$\geqslant$ 68 Gy	340
<68 Gy	37
Field size	
Large field	312
Limited (prostatic) field	65
Treatment technique	
Linear accelerator	362
Co60	15
Previous TURP history	
Previous TURP	131
Only biopsy	246
Co-morbidity	
No co-morbid disease	188
Any co-morbid disease	189

Late toxicity information vas available for the 377 (91%) of the 415 patients randomised. TURP, transurethral prostate resection.

by linear accelerator except for a few patients (4%) who received radiation to the whole pelvis (3.7%) or the limited field of prostatic area with Co60 (0.3%).

2.3. Late toxicity and SAE

Patients were followed every 3 months for 3 years and twice a year thereafter. Long-term toxicity and SAE were evaluated according to the information on the trial follow-up forms and additional data obtained by specific queries sent to the centres to gather more information on the patients with significant toxicities and to clarify the evolution of treatment toxicity. Furthermore, an extensive review of all treatment and follow-up forms was performed by a radiation oncologist and the medical advisor of the EORTC Radiotherapy Group at the EORTC Data Center, in order to detect the occurrence of any event that would fit the definition of SAE currently in use at the EORTC (Table 2). All participating centres were also asked to report any new toxicity or adverse event information that had not yet been forwarded to the EORTC Data Center.

Late toxicity was evaluated according to its effect on the patient's performance and the type of treatment required for symptom relief. The genitourinary (GU), gastrointestinal (GI) late effects and leg oedema were followed and graded according to a 4-point trial specific scale, which is a modification of Radiotherapy and Oncology Group (RTOG) scale [8]. Significant late toxicity was classified as *moderate* (grade 2) when symptoms required prolonged medical treatment occasionally necessitating brief hospitalisation and/or minor surgical intervention; *severe* (grade 3) when treatment required a major surgical procedure or continued hospitalisation (over a month); or *fatal* (grade 4) when there was a toxic death. The time to the onset of late toxicity was measured from the last date of radiotherapy to the day that the most severe toxicity was determined during the follow-up period. We analysed the relationship of late morbidity with a number of pre-treatment and treatment-related factors. Age (>70 years old vs. $\leqslant 70$ years old), field size (large field vs. limited field), radiation treatment technique (Co60 vs. linear accelerator), treatment arm (RT vs. RT and hormone), total dose ($\geqslant 68$ Gy vs. <68 Gy), co-morbid disease and previous transurethral prostate resection (TURP) history were all evaluable parameters (Table 1). The frequencies of late toxicity in relation to these factors were analysed by univanate analysis using the Chi-square test and grouping toxicity in different ways (grade 0 vs. 1 vs. 2 vs. 3–4; grade 0 vs. 1 vs. 2–4; 0–1 vs. 2 vs. 3–4; grade 0–2 vs. 3–4; 0 vs. 1–4) (data not shown).

Sexual dysfunction was assessed through questioning the change in quality of erections, a rather subjective method. Quality of life data relying on self-assessment were not gathered in this trial, since health-related questionnaires and quality of life modules for prostate were not in use for Gu cancer protocols at the time the trial was started.

For several years now, SAE have been monitored in all EORTC studies and reported according to regulatory requirements. However, this system was not yet in place at the time that the EORTC Trial 22863 was started, so the information had to be recalled by the investigators using specific queries. By definition, SAE include grade >2 late treatment toxicity and other additional events that are not defined as a significant toxicity, but still threaten the patient's life (i.e., recurrent bleeding requiring blood transfusions). On the basis of the available information, SAE were grouped as 'likely related', 'assessable' and 'unrelated' in relation to the treatment (Table 2). This three-step scale is currently in use for EORTC protocols and is a modification of the original five-step scale developed by the National Cancer Institute; Common Toxicity Criteria (NCI-CTC). All SAE were included in this analysis.

Table 2
Serious adverse event

A serious adverse event is defined as any undesirable experience occurring in a patient, whether or not it is considered related to the protocol treatment Adverse events that are considered as serious are those which result in:

- Death
- a life-threatening event (i.e., the patient was at immediate risk of death at the time the reaction was observed)
- hospitalisation or prolongation of hospitalisation
- persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- any other medically important condition (i.e., important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above).

In cases where the above events are due to a progression of disease they are not considered SAE

Assessment of causality of SAE

- *Likely related:* There is (some) evidence to suggest a causal relationship to the protocol treatment and the influence of other factors is unlikely or absent.
- *Not assessable:* There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.
- *Unrelated:* There is no evidence of any causal relationship to the protocol treatment.

3. Results

3.1. Late toxicity

Table 3 summarises the type and the incidence of late complications in the 377 patients that were assessable for late toxicity. The complication rates were broken down by grade. Some patients may be listed several times in the table, since they had more than one toxic event during the follow-up period. Most patients (77.1%) had either no or mild (grade 1) late toxicity following treatment. There were 86 (22.8%) patients with grade $\geqslant 2$ urinary or intestinal complications or leg oedema. Of these 86 patients, 72 had grade 2 toxicity, 10 had grade 3 toxicity, and 4 died due to grade 4 toxicity.

The 14 patients (3.7%) with severe (grade $\geqslant 3$) GU & GI toxicity had either severe GU (13 patients) or severe GI complications (1 patient). The 5- and 10- year actuarial rates of severe late toxicity were less than 5% (Fig. 1). The median time to the onset of severe toxicity was 14 months (4–68 months). The status of the grade 3 and 4 complications and the type of medical and surgical interventions are summarised in Table 4. Of these 14 patients, 6 are alive and 8 died, either due to cachexia ($n = 2$) or progression ($n = 2$) or uncontrolled complications ($n = 4$). The four patients with fatal GU complications had urinary obstructions due to urethral or ureteral strictures that caused death in spite of surgical interventions (Table 4). Of the four patients with toxic deaths, two were treated with Co60 and the other two with linear accelerators. Therefore, there were two fatal complications out of 362 patients irradiated with the linear accelerator, whereas there were two fatal complications out of 15 patients irradiated with Co60. The two Co60 patients with fatal toxicity were treated in the same centre with large pelvic fields. Both of these two patients had severe urinary toxicity associated either with significant GI toxicity or severe subcutaneous fibrosis and scrotal oedema.

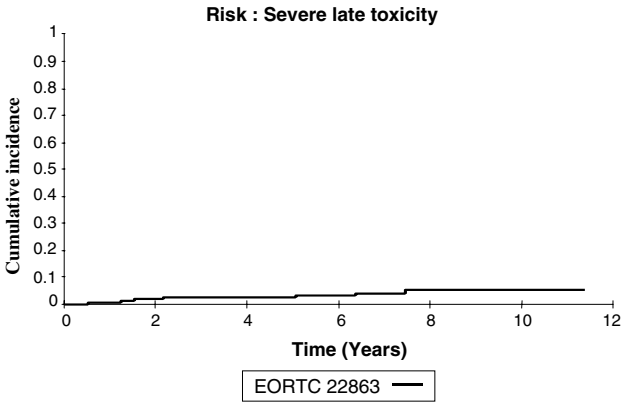

Fig. 1. Actuarial incidence of severe ($\geqslant$ grade 3) late toxicity.

None of the pre-treatment and treatment factors (i.e., age >70 years old vs. $\leqslant$ 70 years old), radiation treatment technique (Co60 vs. linear accelerator), field size (large field vs. small field), treatment arm (RT vs. RT and hormone), total dose ($\geqslant$ 68 Gy vs. <68 Gy, presence of co-morbid disease and previous TURP history) predicted urinary or intestinal toxicity (data not shown).

There was no information about sexual dysfunction in 10% and 12% of the patients who received RT alone or RT and hormonal treatment, respectively. The erectile potency was unchanged (49%), decreased (15%) or lost (26%) in patients who received RT alone, whereas it was unchanged (20%), decreased (6%) or lost (62%) in

Table 3
Incidence of late toxicity by grade

Toxicity	*N* (%)			
	Grade 2	Grade 3	Grade 4	Any significant toxicity ($\geqslant$grade 2)
Cystitis	18 (4.8)	2 (0.5)	0 (0)	20 (5.3)
Hameaturia	18 (4.8)	0	0	18 (4.8)
Urinary stricture	18 (4.8)	5 (1.3)	4 (l.1)	27 (7.2)
Urinary incontinence	18 (4.8)	2 (0.5)	0 (0)	20 (5.3)
Overall GU toxicity	47 (12.5)	9 (2.4)	4 (1.1)	60 (15.9)
Proctitis	31 (8.2)	0	0	31 (8.2)
Chronic diarrhoea	14 (3.7)	0	0	14 (3.7)
Small bowel obstruction	1 (0.3)	1 (0.3)	0	2 (0.5)
Overall GI toxicity	36 (9.5)	1 (0.3)	0	37 (9.8)
Leg oedema	6 (1.6)	0	0	6 (1.6)
Overall toxicity (GU & GI toxicity & leg oedema)	72 (19.1)	10 (2.7)	4 (1.1)	86 (22.8)

• Most of the patients had more than one type of toxicity thus the total at the bottom of the table did not result from simple addition.
• 2 of the grade 4 patients were irradiated with Co60.
• There was not any other significant ($\geqslant$grade 2) toxicity among patients irradiated with Co60 ($n = 15$) except for the 2 patients with grade 4 GU toxicity (stated above) and only 1 patient with grade 2 GI toxicity. GI, gastrointestinal; GU, genitourinary.

Table 4
Fourteen patients with severe (⩾grade 3) late toxicity

RT dose and field size	Grade/Type	Late toxicity	Time to 1st evidence of late toxicity	Evolution
70 SF	3/GU	Urinary stricture requiring unspecified surgery	4 months	Symptoms resolution alter second intervention
		Second unspecified surgery	21 months	Alive NED 60 months
70 SF	4/GU	Bladder neck stricture requiring surgery	4 months	
		Acute pyelonephritis	24 months	Died NED for acute pyelonephritis, at 24 months
70 LF	3/GU	Recurrent urinary stricture requiring uretherotomy	7 months	Bone metastasis at 52 months Alive at 64 months
70 LF*	4/GU	Bilateral pyeloureteral dilatation requiring uretero-cutaneostomy	12 months	
		Second operation of uretero-cutaneostomy	16 months	Died NED at 16 months after second uretero-cutancostoma
70 LF*	4/GU	Ureteral stricture	12 months	
		Uretero-hydronephrosis	17 months	
		Acute pyelonephritis	48 months	Died NED for acute pyelonephritis 48 months
70 SF	3/GU	Urethral stricture required urethrotomy	12 months	Bone met 21 months Alive 34 months
70 LF**	3/GU	Vesico-rectal fistula	14 months	
		Surgery for bladder cancer	15 months	
		Bilateral nephrostomy	20 months	Died NED for cachexia 23 months
70 LF	3/GU	Haematuria requiring TURB and fulguration	14 months	
			23 months	
		Haematuria requiring bladder irrigation	26 months	
		Haematuria requiring TURB and fulguration	90 months	
		Bladder fibrosis and bladder stones requiring lilhotripsy	100 months	
		Permanent external device to collect urine	100 months	Alive NED 100 months
70 LF	3/GU	Severe incontinence requiring ileoureteo cutaneostomy	17 months	
		Rectal bleeding requiring transfusions		Died of metastatic disease 55 months
70 LF	3/GI	Partial colon resection	18 months	
		Partial bowel resection	37 months	
		Severe urethral stenosis not treated surgically	75 months	Alive with bone metastases 84 months
70 LF***	3/GU	Urinary incontinence requiring urinary derivation	25 months	
		Left-uretero-cutaneostomy	49 months	
		Right nephrectomy	50 months	
		Vesico-rectal fistula	56 months	Died NED for cachexia 57months
70 LF	3/GU	Fibrosis of prostatic urethra requiring urethrotomy	45 months	Liver metastasis at 57 months. Local progression and TTJRP at 66 months. Died 71 months
70 SF	3/GU	Urethral stricture requiring urethrotomy	58 months	Improved, Under outpatient therapy Alive NED 77 months
70 LF	4/GU	Renal insufficiency caused by ureteric fibrosis	68 months	Died NED for renal failure at 74 months

LF, large field irradiation; SF, small field irradiation.
NED, no evidence of disease, TURB, trans-urethral bladder resection.
* Patient treated by Co60 unit.
** The patient had concurrent diabetes mellitus. The patient had a second, primary (bladder cancer). The direct cause of death was reported as severe cachexia. and surgical complications.
*** The patient had concurrent diabetes mellitus and hypertension. The direct cause of death was reported as bilateral oedema and hearth failure due to severe cachexia.

patients who received radiation and hormone treatment according to a rough evaluation based on subjective assessment.

In addition to the toxicity evaluation, SAE were also identified and grouped with regard to their relationship with treatment morbidity according to the three-step EORTC scale (Table 2). Thirty-four patients were confirmed to have late SAE according to the EORTC definition. Patients with late SAE were grouped as likely related ($n = 15$), unrelated ($n = 7$) and not assessable ($n = 12$). The 15 likely related events (Table 4) were the 14 cases of severe late toxicity, reported above, and an additional 1 patient with recurrent proctitis requiring blood transfusions. This was considered a treatment-related SAE even though this event is not considered to be *significant* late toxicity according to the trial late toxicity scale.

The seven unrelated events were: myocardial infarction that occurred during treatment ($n = 2$), development of superficial bladder tumours ($n = 3$) and deaths not due to cancer ($n = 2$). These two deaths were one fatal cardio-respiratory insufficiency and one lung embolism, which occurred within 6–14 months from completion of RT treatment without any evidence supporting a relationship between those events and ther protocol treatment.

Table 5 reports on the 12 patients for whom the relationship between the adverse event and the treatment was judged "not assessable", either because of a lack of information or due to a different assessment between the local investigator and the reviewer at the Data Centre. The column "Comments" shows a summary of the available information. The lack of information regarding the cause of death doesn't confirm or preclude that the death was related to GI or GU toxicity. Two patients are also listed in this Table because even though they underwent major bowel surgery after irradiation, the investigators stated that they could not find any evidence of a relationship between the bowel injury and the radiation treatment.

4. Discussion

Toxicity is usually described as an adverse effect that has at least a possible relationship to treatment. Late morbidity encountered from the use of curative doses of definitive prostate irradiation has been a concern and critical when judging the therapeutic ratio of a treatment regimen. In an overview analysis of the RTOG [14], the incidences of significant late toxicity were 6.2% and 2.6% for GU and GI systems, respectively. The severe toxicity rate was 1.5%, most (1.1%) and all of the fatal toxicity being due to GI side-effects [14]. The frequency of severe late toxicity after conventional prostate irradiation was between 0% and 3.6% in other single institutional or multi-institutional series [5,14–19].

The mild toxicity rate in this study was comparable to previously reported ranges. Over two-thirds of the significant urinary toxicity was grade 2. The incidence of all types (haematuria, cystitis, urinary stricture and urinary incontinence) of grade 2 urinary toxicities was similar. Although the overall grade 3 (1.9%) toxicity was comparable to the other series, fatal urinary toxicity (1%)

Table 5
Twelve patients with other SAE for whom the relationship to treatment toxicity was not assessable

RT dose and field size	SAE development	Time to 1st evidence of SAE	Comments
50 SF	Died acute renal insufficiency after RT interruption	2 months	Acute renal insufficiency was pre-existing to RT
70 LF	Died unspecified infectious disease	3 months	During radiotherapy suffered G3 diarrhoea and required bladder catheter
70 LF	Required surgery for bowel perforation	4 months	Died NED 96 months
72 SF	Died suppurative peritonitis after diverticulus perforation	7 months	No evidence of radiation enteritis
70 SF	Died septicaemia	11 months	Prior evidence of grade 2 proctitis, diabetes and bone metastasis
70 LF	Required surgery for perisigmoiditis	13 months	Alive NED 76 months
70 LF	Died NED hydronephrosis	13 months	Follow-up unremarkable
70 LF	Died NED septicaemia	15 months	Grade 2 urinary infections 3 months after RT completion
70 LF	Died unknown causes	50 months	Urinary infections sporadically reported
70 LF	Died internal iliac vein thrombosis	51 months	No evidence of biochemical or local recurrence
60 LF	Died cachexia	56 months	Follow-up unremarkable
70 LF	Died appendicitis	57 months	Follow-up unremarkable

LF, Large field irradiation.
SF, Small field irradiation.
NED, No evidence of disease.

appeared higher than in previous reports [6,10,14,15,19]. Most of the severe and fatal urinary complications resulted from urinary strictures. Half of the patients with $\geqslant$ grade 3 urinary strictures had previous TURP, which was shown to increase the risk of developing urinary stricture by up to 8% [11]. The protocol recommended the use of linear accelerators ($\geqslant$ 10 MV), although Co60 use was not prohibited. Only 15 patients (4%) were irradiated with Co60 and 2 of 15 (13%) had fatal toxicity and these two toxic deaths were treated in the same centre. The fatal toxicity rate in patients irradiated with linear accelerator was 0.6% (2 of 362 patients). The rate as well as the average latency for significant late toxicity of the linear accelerator patients was in agreement with data from previous reports [6,10,14,15,19–21].

Urinary incontinence was evaluated according to the trial-specific scale. Significant incontinence was detected in 5.3% and only 0.5% had severe toxicity that required major surgery. The frequency of incontinence has been reported to be between 0% and 3% in previous series [10,15,17,22,23]. Incontinence rates vary in other series due to the somewhat different definitions and the history of previous transurethral surgery. The RTOG late morbidity scale did not address incontinence; therefore its frequency was not reported frequently in the publications where the RTOG scale was used.

Overall, in our series, severe GU events were more frequent than severe GI events. Most studies of curative prostate irradiation have focused on the increase of intermediate and severe GI toxicity rather than GU toxicity [6,16,20]. However, a similar report emphasising GU toxicity has recently been reported [24]. These relatively high incidences of severe GU toxicity may be attributed (in part) to previous TURP and (in part) to the fact that our analysis was based on extensive queries into the details and causative factors of each adverse effect, in addition to routine follow-up information. This led to more accurate and less subjective information, that was not biased by the concurrent age-related and disease-related pathologies.

The cumulative incidence of significant GI morbidity (9.2%) in our trial is less than comparable previous reports reported in the RTOG and other series [6,14,15,19]. There was only one patient with grade 3 GI toxicity, who had partial bowel resections and died due to the associated GU toxicity. Proctitis was the most frequent recto-sigmoid morbidity, as was also observed in the series of Lawton and colleagues and Perez and colleagues [16,25].

The rate of erectile impotence was much higher in the arm where patients received RT and hormone treatment according to the physician's rough assessment. Sexual dysfunction was not assessed rigorously through organ-specific quality of life questionnaires in this trial, since the role of quality of life analyses was not well established in the 1980s when this protocol was started.

In addition to the toxicity analysis, we focused on reporting the occurrence of SAE, which covers the late complications that are reported above and additional events that seem not to be directly related to toxicity. No similar analysis has been reported before for a RT series, probably because SAE reporting is considered to be an instrument to detect the unexpected consequences of systemic treatments, whereas radiation therapists usually focus on dose-related local toxicity. When large treatment fields are employed, as in our series, a substantial dose is delivered to several organs surrounding the target volumes. The use of SAE reporting is particularly suitable to address the occurrence of events that are not clearly related to treatment and that would usually not be considered in the toxicity reports. It is well known that, as time elapses since the end of the treatment, follow-up visits to the treating institution become less frequent. Besides, information on adverse events may be filtered by general practitioners or physicians of other hospitals. With prolonged intervals from treatment completion, another source of bias may also occur; the symptoms attributed to treatment side-effects in reality may be totally, or at least partially, due to undetected disease progression or to other concomitant illnesses. This may be particularly so in an elderly population, such as prostate cancer patients, as it has been reported that age-matched control groups are affected by significant urinary and GI problems [9,26]. As a consequence, concomitant pathologies and treatment morbidity may act together and the partial role of each causative factor cannot be ascertained. For similar reasons, the assessment of the possible causes of death in prostate cancer patients has been reported to vary between expert observers by as much as 66% [27]. Subjectivity in the assessment of events is therefore unavoidable. The SAE reporting process to regulatory agencies aims to reduce this subjectivity in the evaluation of events in which multiple causes may act together or detailed information is lacking. For this reason, we also considered the events reported as 'not assessable' or 'not related' that would normally not be included in a toxicity series.

Our analysis was based on follow-up information collected from the follow-up forms of this prospective EORTC trial, as well as from comprehensive queries.This led to an increase in the information collected for long - term treatment toxicity and other late SAE. Although four (1%) late treatment, related deaths occurred, long-term toxicity was limited, with less than 5% grade, 3 or 4 late complications being reported. The data in this study can be used as a baseline for comparison with irradiation techniques currently in use in the EORTC prostate protocols, such as 3D-conformal radiotherapy or intensity modulated radiotherapy (IMRT). It

is of obvious importance to have an accurate knowledge of the possible consequences to aid in decision-making and counselling of the patient.

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