Hypofractionated radiation therapy versus conventional radiation therapy in prostate cancer: A systematic review of its safety and efficacy

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Prostate cancer; Radiation therapy; Hypofractionation; Systematic review

Abstract
Context: New therapeutic alternatives can improve the safety and efficacy of prostate cancer treatment.
Objectives: To assess whether hypofractionated radiation therapy results in better safety and efficacy in the treatment of prostate cancer.
Acquisition of evidence: Systematic review of the literature through searches on PubMed, Cochrane Library, CRD, ClinicalTrials and EuroScan, collecting indicators of safety and efficacy. Synthesis of the evidence: We included two systematic reviews and a clinical trial. In terms of efficacy, there is considerable heterogeneity among the studies, and no conclusive results were found concerning the superiority of the hypofractionated option over the normal fractionated option. In terms of safety, there were no significant differences in the onset of acute genitourinary complications between the two treatments. However, one of the reviews found more acute gastrointestinal complications in patients treated with hypofractionated radiation therapy. There were no significant differences in long-term complications based on the type of radiation therapy used, although the studies did have limitations.
Conclusions: To date, there are no conclusive results that show that hypofractionated radiation therapy is more effective or safer than normal fractionated radiation therapy in the treatment of localized prostate cancer.

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Introduction

Prostate cancer (PCa) is one of the main health problems in the male population. It is a rare malignancy in men younger than 50 years old, the age from which its incidence increases, with 90% of cases being detected in men over age 65. Its etiology is unclear, although we do know that it is associated with environmental exposures, lifestyles, a prior family history and genetic factors.1,4

In Spain, PCa ranks second in the general population, with an incidence of 12.9%, behind colorectal cancer (15%) and ahead of lung (12.4%) and breast tumors (11.7%). If we take into consideration the male population alone, the highest incidence corresponds to PCa (21.7%), followed by lung cancer (16.9%). The 5-year prevalence rate is also the highest one (31.4%) followed by colorectal cancer (16.4%).3,4

In absolute terms, cancer represents the first cause of death in Spain. PCa ranks fifth with respect to the general population with a mortality rate of 5.3%, behind lung (20.6%), colon and rectum (14.3%), breast (5.9%) and pancreas (5.6%) tumors. In males, mortality from PCa ranks third (8.6%) behind mortality caused by lung (27.4%) and colorectal (13.7%) tumors.3,4

PCa can be classified in different ways: according to tumor extent (TNM), histopathological grade (Gleason), clinical or histopathological stage and according to risk.2,9 Once it has been diagnosed and the stage of the disease has been determined, there are several strategies for its clinical management, regarding initial treatment choice, the volume to be treated with radiotherapy (RT) if this therapeutic modality is chosen or clinical management after treatment. Any clinical-practice guideline on treatment of PCa includes information on the different treatment options depending on the clinical or pathological stage, with grades of evidence and recommendations in compliance with the criteria of the SIGN group.10

Treatment options, depending on the characteristics of each tumor, may range from expectant management of the disease to prostatectomy. RT is one of the major therapeutic pillars for clinically localized PCa, particularly external radiation therapy alone or in combination with androgen deprivation therapy. However, optimal fractionation and total treatment time for PCa irradiation remain a matter of debate. It has been traditionally administered at fractions of around 1.8–2.0 Gy, 5 days a week for 8–9 weeks.11,12 The total administered dose is usually 70–80 Gy.12,13 In the past few decades, a new form of administering RT has emerged, hypofractionated RT, which is based on the delivery of higher doses per fraction during a smaller number of fractions, thus getting a lower total dose than in the case of RT with standard fractionation. In particular, hypofractionated RT in PCa involves administering a single-fraction radiation dose >2.1 Gy, 4 or 5 days a week, for 4–5 weeks. The total radiation dose in hypofractionated RT ranges between 52.5 and 72 Gy.12,14,16

The use of hypofractionated RT in PCa is justified by the fact that there is a dose–response relationship and a high sensitivity to the dose administered per fraction.17,18 Hypofractionated RT could be more advantageous than conventional RT, since it would enable us to improve tumor control and to reduce radio-induced toxicity.17 It could also offer other advantages, such as resource optimization, cost reduction and an improvement of the quality of life of the patient.12,13,19 However, some studies have shown inconsistent findings regarding efficiency and safety when comparing both RT modalities, so an analysis of the available evidence...
Hypofractionated radiation therapy versus conventional radiation

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Search strategy and databases used.</th>
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<tr>
<td><strong>Search strategy</strong></td>
<td><strong>Databases</strong></td>
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<tr>
<td>3. #1 AND #2</td>
<td>Medline (PubMed)</td>
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</table>

is required. The aim of this review was to assess the efficiency and safety of hypofractionated RT for the treatment of prostate cancer.

**Methods and materials**

A systematic review (SR) of scientific literature was conducted. The identification of studies was performed through a search of scientific literature on databases: MEDLINE (PubMed), The Cochrane Library and Databases of the Center for Reviews and Dissemination ([CRD], University of York, United Kingdom). Searches were also carried out in other databases such as Clinicaltrials and EuroScan. Search strategies were designed (Table 1) for the identification of studies using free and controlled terminology, adapting each term to the thesaurus of each database, in order to obtain higher sensitivity and specificity in the result. Internet searches were also conducted of websites of specialty scientific societies associated with the topic and of health technology assessment agencies at both national and international levels in order to locate health technology assessment reports if available. A manual review of bibliographical references in the documents found was also conducted in order to locate studies which were not identified in the electronic search.

The search strategy was developed on 30 May, 2014 and no publication date restrictions were applied. We included clinical trials published in English, Spanish or French on patients with PCa treated with hypofractionated RT versus conventional RT. We excluded duplicate studies or those that had been outdated by subsequent studies from the same institution, narrative reviews, letters to the editor, comments, editorials, studies on one specific case, studies published in languages other than English, Spanish or French, cohort studies, case series and non-randomized studies (Appendix B – additional material).

Performance indicators were collected as outcome measures: biochemical failure-free survival (BFFS) as defined by the criteria of the American Society for Therapeutic Radiology and Oncology (ASTRO) as three consecutive elevations above the nadir value or as defined by the Radiation Therapy Oncology Group (RTOG) in Phoenix (ASTRO-Phoenix criteria) which defines biochemical failure as an elevation of 2 points above the nadir value of the biochemical failure rate (BFR), the prostate-specific antigen (PSA) level, the survival rate and of any other efficiency variable included in the studies.

We collected the occurrence of acute adverse effects in the long term, their location and severity, particularly gastrointestinal and genitourinary complications, as safety indicators. Acute toxicity is normally assessed using the classification provided by the RTOG/European Organization for Research and Treatment of Cancer (EORTC). Long-term toxicity is defined as symptoms occur or last for 6 months or more after RT, as assessed using the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT/SOMA) scoring system.

The selection and review of studies were carried out by two reviewers independently. A first selection of studies was made by reading the title and abstract, and those who met the inclusion criteria were revised by reading the full text. Discrepancies and doubts were resolved by consensus or in collaboration of another member of the research team. Tables were made detailing the studies included in and excluded from the review, justifying the cause for exclusion. The quality of evidence was assessed using the scoring system of the Medical Center based on the Oxford evidence criteria. The evidence assessment process was carried out by two reviewers independently. Discrepancies among researchers were resolved by intervention of a third researcher or by consensus. The data of the selected studies were extracted by two reviewers independently, using a data extraction sheet which had been specifically developed for this review. Data collection included information on bibliographic data, study characteristics, patient characteristics and measurement of results with regard to the efficiency and safety of the procedure.

**Results**

In a first phase, 286 studies were detected. After reading the title and abstract, 224 studies were excluded for not meeting the inclusion criteria. After a full reading of the 62 papers that initially met the inclusion/exclusion criteria, 59 publications were excluded (Appendix B – additional material), with three articles being eventually selected, one of which was a randomized clinical trial (RCT) and two of which were a SR or a meta-analysis. The flow diagram of the studies included and excluded is shown in Fig. 1.

Besides, two ongoing RCTs were found: the Prostate Fractionated Irradiation Trial (PROFIT) (NCT00304759), aiming at checking if a 8-week RT program (7800 cGy in 39 sessions, 8 weeks) can be safely compressed into a 4-week treatment (6000 cGy in 20 sessions, 4 weeks) with similar efficiency and the Radiation Therapy in Treating Patients With Stage II Prostate Cancer (NCT00331773), aiming at comparing several RT regimens in treating patients with Stage II PCa.

The two SRs provide a level of evidence 1a (recommendation level A) and the RCT11 provides a level of evidence 1b (recommendation level A) according to the scoring system.
of the Medical Center based on the Oxford evidence criteria for treatment studies (Table 2).

The SR and meta-analysis carried out by Botrel et al. compares the efficiency and side effects of hypofractionated RT versus conventional RT in treating patients with localized PCa and no metastases. This review includes nine RCTs with a total of 2702 patients and a median follow-up in the studies ranging from 1 to 7.5 years. The characteristics of the studies included are shown in Table 3.

The SR by Zaorsky et al. compares the results of phase III studies with hypofractionated RT versus phase III studies with escalating doses of RT at a conventional fractionation dose. It includes five of the nine RCTs already included in the SR by Botrel et al., conducted on patients with localized PCa (T1–T2 N0–Nx, M0) and with locally advanced PCa (T3–T4 N0–Nx, M0), with a total of 1828 patients and a median follow-up ranging from 35 to 90 months. The characteristics of the studies included are shown in Table 3.

The RCT by Hoffman et al. aims at comparing the toxicity results in the long term of normofractionated RT versus hypofractionated RT in PCa and at identifying dose and clinical parameters associated with long-term toxicity after treatment with hypofractionated RT on 222 patients with prostate adenocarcinoma confirmed by biopsy, cT1b-cT3b, with good performance status (≤2 Zubrod, PSA ≤ 20 ng/ml, Gleason ≤ 10), with no clinical or radiographic evidence of metastatic node or bone involvement. The characteristics of the study are shown in Table 3.

### Efficacy results

The results of the SR by Botrel et al. show that BFSS is similar in both groups: fixed-effect meta-analysis with a hazard ratio of 1.03 (CI 95%: 0.88–1.20; p = 0.75), showing high heterogeneity ($X^2 = 15.32$, df = 2; $I^2 = 87%$; $p = 0.0005$). BF is similar in both groups: fixed-effect meta-analysis with a relative risk (RR) of 0.99 (CI 95%: 0.87–1.12; $p = 0.85$) with moderate heterogeneity ($X^2 = 7.94$, df = 5; $I^2 = 37%$; $p = 0.16$). The mortality rate from cancer does not differ between both groups: fixed-effect meta-analysis with a RR of 0.34 (CI 95%: 0.09–1.23; $p = 0.1$) (Table 4).

The results of the SR by Zaorsky et al. show significant differences in terms of BFSS in two studies, one in favor of the control group with rates of 60% for conventional RT versus 53% for hypofractionated RT and another one in favor of the intervention group, with rates of 79% for conventional RT versus 85% for hypofractionated RT ($p = 0.035$). The other three studies show non-significant results (Table 4).

### Safety results

In the SR by Botrel et al., the incidence of acute gastrointestinal complications (grade ≥ 2) was higher in the hypofractionated RT group: fixed-effect meta-analysis with a RR of 2.02 (CI 95%: 1.45–2.81; $p < 0.0001$) with moderate heterogeneity ($X^2 = 7.47$, df = 5; $I^2 = 33%$; $p = 0.19$). In a meta-analysis undertaken by using a random-effects model, the results were favorable to conventional RT with a RR of 1.87 (CI 95%: 1.20–2.93; $p = 0.006$). Acute genitourinary complications (grade ≥ 2) were similar in both groups: fixed-effect meta-analysis with a RR of 1.19 (CI 95%: 0.95–1.49; $p = 0.13$) with moderate heterogeneity ($X^2 = 5.83$, df = 4; $I^2 = 31%$; $p = 0.21$) (Table 4). The incidence of long-term gastrointestinal complications was similar in both groups: fixed-effect meta-analysis with a RR of 1.17 (CI 95%: 0.79–1.72; $p = 0.44$) with no heterogeneity ($X^2 = 3.74$, df = 5; $I^2 = 0%$; $p = 0.59$). The incidence of long-term genitourinary complications was similar in both groups: fixed-effect meta-analysis with a RR of 1.16 (CI 95%: 0.80–1.68; $p = 0.44$) with no heterogeneity ($X^2 = 2.73$, df = 4; $I^2 = 0%$; $p = 0.60$) (Table 4).

The SR by Zaorsky et al. shows that acute complications are similar in both groups in three of the five studies included. One study shows more toxicity in the case of hypofractionated RT and another study finds significantly more gastrointestinal complications in the hypofractionated group in weeks 2–4 (Table 4).

The results of the RCT by Hoffman et al. show no differences in long-term genitourinary complications (grade ≥ 2), with rates of 16.5% in the control group versus 15.8% in the intervention group ($p = 0.97$). With regard to long-term complications, the results were not statistically significant ($p = 0.88$).

### Table 2

Quality of evidence and grade of recommendation according to the scale of the Centre for Evidence-Based Medicine of Oxford for treatment studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Level of evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botrel et al., 2013</td>
<td>Systematic review</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Zaorsky et al., 2013</td>
<td>Systematic review</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Hoffman et al., 2014</td>
<td>Randomized clinical trial</td>
<td>1b</td>
<td>A</td>
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</tbody>
</table>
Hence includes In 20,21 although mentioned good and cost. Various studies analyzing radiotherapy; conventional radiotherapy; HRT, hypofractionated radiotherapy; ND, no data.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Study design</td>
<td>SR and meta-analysis</td>
<td>SR</td>
<td>RCT</td>
</tr>
<tr>
<td>Included studies</td>
<td>9 RCT</td>
<td>5 RCT</td>
<td>–</td>
</tr>
<tr>
<td>N* of patients</td>
<td>2702 (HRT: 1450)</td>
<td>1828 (HRT: 910)</td>
<td>222 (HRT: 111).</td>
</tr>
<tr>
<td>Study population</td>
<td>Localized PCa T1–T4</td>
<td>SD</td>
<td>Prostate + proximal seminal vesicles</td>
</tr>
<tr>
<td>CTV</td>
<td>Prostate + seminal vesicles (total or partial)</td>
<td>SD</td>
<td>CTV + 10–15 mm around except in the back side (4–8 mm)</td>
</tr>
<tr>
<td>PTV</td>
<td>CTV + 8.8–1.0 cm</td>
<td>Heterogeneous</td>
<td>Variable</td>
</tr>
<tr>
<td>Hormone treatment</td>
<td>Yes in 6 studies</td>
<td>SD</td>
<td>28% low risk</td>
</tr>
<tr>
<td>Risk groups</td>
<td>Heterogeneous</td>
<td>Heterogeneous</td>
<td>71% intermediate risk</td>
</tr>
<tr>
<td>Intervention</td>
<td>RT 2D, 3D, IMRT</td>
<td>RT. Excludes brachytherapy and SBRT</td>
<td>IMRT</td>
</tr>
<tr>
<td>Treatment intervention</td>
<td>16–30 fractions of 2.4–4.5 Gy</td>
<td>20–30 fractions of 2.4–3.1 Gy</td>
<td>72 Gy in fractions of 2.4 Gy</td>
</tr>
<tr>
<td>Treatment control group</td>
<td>32–42 fractions of 1.8–2.0 Gy</td>
<td>32–42 fractions of 1.8–2.0 Gy</td>
<td>75.6 Gy in fractions of 1.8 Gy</td>
</tr>
<tr>
<td>Total dose intervention</td>
<td>52.5–72 Gy</td>
<td>52.5–70.2 Gy</td>
<td>72 Gy in fractions of 2.4 Gy</td>
</tr>
<tr>
<td>Total dose control group</td>
<td>64–80 Gy</td>
<td>64–80 Gy</td>
<td>75.6 Gy in fractions of 1.8 Gy</td>
</tr>
<tr>
<td>Length of intervention</td>
<td>4–5 weeks</td>
<td>6.5–8 weeks</td>
<td>SD</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of control group treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up (median)</td>
<td>1–7.5 years (1 study &lt; 2 months)</td>
<td>35–90 months</td>
<td>6 years (range 0.8–11.4)</td>
</tr>
</tbody>
</table>

PCa, prostate cancer; CTV, clinical target volume; RCT, randomized clinical trial; PTV, planned target volume; SR, systematic review; RT, radiotherapy; CRT, conventional radiotherapy; HRT, hypofractionated radiotherapy; ND, no data.

gastrointestinal complications (grade > ) differences do exist between both groups with rates of 5.1% in the control group versus 10.0% in the intervention group, although this difference does not reach statistical significance (p = 0.11) (Table 4).

Discussion

Various studies carried out in recent years have shown good results with hypofractionated RT in patients with PCa.10,34,35 Hence the idea that hypofractionated RT might be superior to conventional RT, and that it could be the standard radiotherapy treatment for these patients. Under this assumption, the use of hypofractionated RT instead of conventional RT would imply more tumor control, an improved quality of life of the patient and a lower treatment cost.12,13,24

We have found two SRs analyzing the efficiency and safety of hypofractionated RT versus conventional RT.12,13 Similarly, we have found a RCT, which was not included in the above-mentioned SRs, focusing on the safety of the procedure, and analyzing the long-term complications of hypofractionated RT.11 All the studies analyze the effects of moderate hypofractionation. The SR by Botrel et al.13 includes nine RCTs and carried out a meta-analysis, and the SR by Zaorsky et al.12 includes five RCTs, which are also included in the first SR. Despite this, the information gathered in each SR varies and data do not entirely coincide. In our study, we have collected the information provided by the authors in each of the SRs.

With regard to the efficiency of hypofractionated RT, the SRs show that there are no conclusive results on the superiority of hypofractionation as compared to normofractionation. However, the SRs show great heterogeneity between the studies. There are differences in the study population, including different PCa stages and different risk groups. There are differences with regard to intervention, RT doses and length of treatment, as well as in the margins of the target volume. Concomitant hormonal therapy is equally variable, and the studies show different outcome measures.12,13

The outcome variables most commonly analyzed in the RCTs included in the SRs are BFFS and BF, although the definition criteria for these variables vary among studies. The most frequently used criteria to assess PSA failure are ASTROZ0 and ASTRO-Phoenix,21 although it is estimated that BFFS rates can vary up to 20% depending on the definition used.26 The definition provided by the ASTRO-Phoenix criteria is currently the preferred one since it is considered to be more sensitive and specific.20,21 In the SRs found, it is difficult to assess the mortality rate for each therapeutic choice, since there are no trials available with a sufficiently long follow-up period. Mortality and overall survival are the variables of greatest interest when assessing a treatment for any kind of cancer.13

The safety of hypofractionated RT is considered to be a fundamental aspect given the proximity of healthy
Table 4 Results found in the studies included in the three selected works.

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<tr>
<td>FFFB</td>
<td>3 studies collect this datum. Similar in both groups HR: 1.03; 95% CI = 0.88-1.20 (p = 0.75), with HH (I² = 87%)</td>
<td>In 2 of the 5 studies, there are significant differences (p &lt; 0.05), one in favor of the control group and another one in favor of the intervention group</td>
<td>SD</td>
</tr>
<tr>
<td>BF</td>
<td>6 studies collect this datum. Similar in both groups RR: 0.99; 95% CI = 0.87-1.12 (p = 0.85), with MH (I² = 37%)</td>
<td>Similar in both groups</td>
<td>SD</td>
</tr>
<tr>
<td>Rate of mortality of tumor</td>
<td>5 studies collect this datum. Similar in both groups RR: 0.34; 95% CI = 0.09-1.23 (p = 0.10)</td>
<td>ND</td>
<td>SD</td>
</tr>
<tr>
<td>PSA nadir</td>
<td>2 studies collect this datum. Similar in both groups (≤0.5 ng/mL)</td>
<td>ND</td>
<td>SD</td>
</tr>
<tr>
<td>Acute complications*</td>
<td>6 studies collect this datum. Similar in both groups. RR: 1.19; IC95% = 0.95-1.49 (p = 0.13), with MH (I² = 31%)</td>
<td>Similar in both groups</td>
<td>SD</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Higher incidence in HRT group. RR: 2.02; 95% CI = 1.45-2.81 (p &lt; 0.0001), with MH (I² = 33%)</td>
<td>1 study finds a significantly higher percentage in HRT group</td>
<td>SD</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 studies collect this datum</td>
<td>NS. Except for 1 study with higher percentage in the intervention group (p = 0.028)</td>
<td>No differences between groups. 16.5% control group vs 15.8% Intervention group (p = 0.97)</td>
</tr>
<tr>
<td>Long-term complications*</td>
<td>Similar in both groups. RR: 1.16; 95% CI = 0.80-1.68 (p = 0.44), NH (I² = 0%)</td>
<td>NS</td>
<td>Not significant difference between groups. 5.1% control group vs 10.0% intervention group (p = 0.11)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Similar in both groups. RR: 1.17; 95% CI = 0.79-1.72 (p = 0443), NH (I² = 0%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Similar in both groups. RR: 1.17; 95% CI = 0.79-1.72 (p = 0443), NH (I² = 0%)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

FFBF, failure-free biochemical survival; BF, biochemical failure; HR, hazard ratio; SD, no data; HRT, hypofractionated radiotherapy; NS, not significant; NH, no heterogeneity; MH, moderate heterogeneity; HH, high heterogeneity.

* Complications grade ≥2 according to the RTOG/EORTC scale.

tissue such as the rectum or the bladder in the area to be irradiated. The RCTs analyze the potential gastrointestinal and genitourinary complications, both acute and in the long term. Acute complications are usually classified according to the RTOG/EORTC scoring system and studies include those that are grade >2, which are of particular interest since they require treatment. However, for some authors, the RTOG scoring system has certain limitations, since it does not include the assessment of some anorectal symptoms such as the urge to defecate and fecal incontinence. With regard to acute complications, the two SRs do not show significant differences in the occurrence of genitourinary complications between both treatments. However, one of the SRs finds more acute gastrointestinal complications in patients treated with hypofractionated RT. Despite this, the authors maintain that there are limitations, and, given the limited number of studies, further research is deemed necessary. The long-term complications of hypofractionated RT raise particular concern given the lack of information on long follow-up periods. The SRs include those rectal or urinary problems occurring or lasting for 6 months after radiotherapy ends as late complications. The SRs do not find significant differences in late complications depending on the type of RT used. However, long-term information is limited, and one must take into account that radiation-induced effects might occur years after treatment ends. Hoffman et al. consider those complications occurring from 90 days after radiotherapy onwards as long-term complications. With a 6-year follow-up, this study finds that treatment with escalating doses and a hypofractionated regimen is safe, with limited grades 2–3 complications in the long term. However, the authors are cautious due to the limitations of the study, among others the fact that it was conducted in a single center, with a single hypofractionated regimen and with a limited number of cases.
So far, we could say that no conclusive results have been published on the efficiency and safety of hypofractionated RT for treating PCs. For Botrel et al., the lack of evidence on long-term results represents one of the main obstacles for hypofractionation to be regarded as a standard treatment choice. Zaorski et al. claim that, in the absence of evidence, hypofractionation should be used in the context of clinical trials only. In this regard, the National Comprehensive Cancer Network does not provide recommendations on hypofractionated treatment regimens since hypofractionated RT is considered to be an emerging therapy which has not been established so far.

There are currently two ongoing RCTs aiming at shedding light on the best hypofractionated RT regimen (NCT00304759 and NCT00331773). In theory, this treatment would provide greater comfort for the patient, organizational improvements and a reduced cost to the healthcare system. However, we have found no cost-effectiveness studies assessing hypofractionated RT versus conventional RT. Only one study estimates the significant saving that hypofractionation would entail to the patient with fewer hospital visits and the consequent saving in travel time and parking. Nor have we found any study including measures of quality of life of patients depending on the type of RT used, studies which would be of great interest.

It is important to take into account that there are, in addition to hypofractionation, other RT modalities, such as high-dose-rate brachytherapy or stereotactic body RT which could be therapeutic alternatives to hypofractionated RT. In the near future, besides, we might develop models combining specific biomarkers with preclinical variables, in such a way that fractionation schemes would be personally established for each patient with outcome prediction.

We can therefore conclude that regarding hypofractionated RT, SRs do not find significant differences and neither regarding acute genitourinary complications. However, due to the limitations of the studies and their limited number, further research is required. The studies on the long-term risks of hypofractionated RT do not find significant differences either. However, long-term information is limited, so there is not enough scientific evidence available on the late effects of this therapeutic modality.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acuroe.2015.05.003.

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