ORIGINAL ARTICLE

Second neoplasm after treatment of localized prostate cancer

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KEYWORDS
Prostatic neoplasm; Prostate cancer; Treatment; Radical prostatectomy; Radiotherapy; Second neoplasm; Systematic review of the literature

Abstract

Introduction: Prostate cancer (PC) treatment in early stages is radical prostatectomy (RP) or external radiotherapy (ER). There is some uncertainty regarding the development of new ER induced malignant tumors or second primary tumor (SPT), a fact influencing the choice of therapy. The purpose of this study is to determine the best therapeutic alternative for localized PC, in regards to incidence and time of development.

Material and methods: A systematic review of the literature is proposed by means of evaluation of studies conducted with localized PC and treated with RP or ER, published between 1990 and 2010. The Mega searchers used were Cochrane Library and Trip Database, and the databases used were MEDLINE, OVID, Science Direct, Scielo and Lilacs, using MeSH terms and free words. The studies selected were analyzed using the MINCIR score of methodological quality (MQ) to compare articles with different design. The variables were considered to be number of patients treated, localization of lesions, global incidence of SPT and MQ of the studies. Averages, medians and weighted averages (WA) were calculated. The study groups were compared using the 95% confidence intervals of the medians.

Results: Eleven articles fulfilled the screening criteria (retrospective cohorts and case series); providing 13 series for the study. The average of MQ was 14.7 points (13 and 16 points). The most frequent localizations of SPT were bladder, rectum and long. The WA of the global incidence of SPT for the series was 3.6% (4.1% for ER and 2.2% RP).

Conclusion: The information existing did not make it possible to demonstrate an association between the appearance of SPT and therapies for localized PC, even though there was a superior tendency in irradiated patients.

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PALABRAS CLAVE
Neoplasia prostática; Cáncer de próstata; Tratamiento; Prostatectomía radical; Radioterapia; Segunda neoplasia; Revisión sistemática de la literatura

Segunda neoplasia tras el tratamiento del cáncer prostático localizado

Resumen
Introducción: El tratamiento del cáncer prostático (CP) en estadíos precoces es la prostatectomía radical (PR) o la radioterapia externa (RE). Existe incertidumbre respecto del desarrollo de nuevos tumores malignos o segundo tumor primario (STP) inducidos por RE, hecho gravitante en la elección de la terapia. El objetivo de este estudio es determinar la mejor alternativa terapéutica para CP localizado, en lo que respecta a la incidencia y tiempo de desarrollo de STP.

Material y método: Se plantea una revisión sistemática de la literatura mediante la evaluación de estudios realizados con CP localizado y tratado con PR o RE, publicados entre 1990 y 2010. Se utilizaron los Mega buscadores Cochrane Library y Trip Database, y las bases de datos MEDLINE, OVID, Science Direct, ScIELO y LilACS, empleando términos MeSH y palabras libres. Los estudios seleccionados fueron analizados utilizando el escore MINCIR de calidad metodológica (CM) para comparación de artículos con diferente diseño. Se consideraron las variables número de pacientes tratados, localización de lesiones, incidencia global de TSP y CM de los estudios. Se calcularon promedios, medianas y promedios ponderados (PP). Se compararon los grupos en estudio utilizando intervalos de confianza del 95% de las medianas.

Resultados: 11 artículos cumplieron los criterios de selección (cohortes retrospectivas y series de casos); aportando 13 series para el estudio. El promedio de CM fue 14.7 puntos (13 y 16 puntos). Las localizaciones más frecuentes de TSP fueron vejiga, recto y pulmón. El PP de la incidencia global de TSP para las series fue de 3.6% (4.1% para RE y 2.2% PR).

Conclusion: La información existente no permite demostrar asociación entre aparición de TSP y las terapias para CP localizado, a pesar de que existe una tendencia superior en pacientes irradiados.

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Introduction
Prostate cancer (PC) usually occurs in men over 50 years and has become more important worldwide due to the progressive increase in the incidence and mortality, constituting the fourth malignancy among men. In Chile, the incidence of PC is unknown, but it has been estimated at 55–57 cases per 100,000 males. In the meantime, mortality has experienced a permanent and progressive increase and now stands as the second leading cause of cancer death in men, with a mortality rate of 20.2 per 100,000.

In localized stages (I and II), radical surgery is the standard treatment, external radiotherapy (ER) may also be performed, associated or not with hormone-blocking therapy. However, there is no conclusive evidence of the superiority in terms of survival of either technique. In recent years, brachytherapy has been incorporated as a therapeutic alternative.

Radical prostatectomy (RP) is the complete removal of the prostate and the seminal vesicles. The most important complications are erectile dysfunction (29–100% of patients) and urinary incontinence, mild (4–50% of patients), and severe (0–15% of patients). Currently, there are three types of ER (conventional, three-dimensional conformal, and of modulated intensity), and this evolution has made it possible to increase the doses with less damage to nearby tissues and organs. The complications occur mainly at the level of the rectum and bladder, highlighting initially inflammatory problems and subsequently the atrophic and degenerative changes of neighboring tissues (anal, urethral stenosis, and fistula development).

There is some consensus that RP and ER are comparable in PC control, even in terms of morbidity and quality of life one year after the treatment. The high survival of PC in early stages has generated a new variable to consider, which are late complications among which is the possibility that ER can induce the occurrence of other tumors, known as second malignancy or secondary primary tumor (SPT).

A latency period of at least 5 years is accepted for the development of radiation-induced SPT. It is also accepted that variables such as patient’s age, the target organ, the dose used, the extent of irradiated tissue, and the type of radiotherapy are crucial to its development. However, the incidence of radiation-induced tumors was underestimated because of the short survival associated with the old radiotherapy; but, with the technological advancement, there have been substantial improvements in survival with radiotherapy that usually exceed 15 years or more. This has allowed us to quantify a cumulative incidence of SPT of up to 20%.

There are currently at least three narrative reviews related to the subject, which include the personal view of the author or authors regarding the situation, although there is no systematic review to summarize and organize the available evidence regarding this uncertainty. The objective of this study is to determine the best therapeutic option for patients with localized PC (RP or ER), in terms of incidence and time of development of SPT. The methodology of this manuscript was based on the PRISMA initiative for conducting systematic reviews and meta-analyses.
Material and methods

A systematic review of the literature was carried out, performed as the topic of the postgraduate thesis of the master’s program in Medical Sciences at the Universidad de La Frontera, year 2011. We included articles of all kinds of designs of clinical research, which considered the treatment of patients with PC by means of ER and/or RP, with a follow-up of 5 years or more, to assess the occurrence of SPT, without language restriction and published between 1990 and 2010. Contaminated items were excluded with patients with other concomitant malignancies or previous to the diagnosis of PC, as well as the contaminated items with PC patients treated with therapies other than RP and ER or combined.

As sources of information, we used the Cochrane Library and Trip Database mega-seekers and the SciELO, OVID, MEDLINE, LILACS, and Science Direct databases. The last search for information was made in December 2010. We applied the following MeSH terms: Prostatic Neoplasms, Neoplasms, Second Primary, Prostatic Neoplasms/radiotherapy, and Prostatic Neoplasm/therapy. Furthermore, we applied the following free terms: Radical Prostatectomy, External beam radiation, and Radiation Therapy. This way, we performed a highly sensitive search, using the 'DNA' Boolean connector, in order to avoid loss of articles. The screening of the studies was conducted by practicing the following order: by title, then by abstract, and finally by extension; to which finally the ad-hoc critical reading guidelines were applied.

The data were collected on a template, which was completed by two independent investigators (EA, PA), masking the authors and centers of origin of the studies, as well as the journals and publication years of each study. The ER and PR results were evaluated according to the occurrence of the SPT, considering time of occurrence and location of the second neoplasm. In addition, we evaluated the type of radiotherapy used and the dose employed. We also evaluated the methodological quality (MQ) of the primary studies applying the MinCir score to all of them, which assesses the study design, study population, and methodology employed by means of a score of 6–36 points, with a cut-off of 18 points to define MQ. 18

We calculated the weighted average (WA) of the relative risks (RR) using the PP<sub>GT</sub> = ΣX<sub>i</sub> × e<sub>i</sub> / Σe<sub>i</sub> formula (where X<sub>i</sub> is the value of the study variable i; e<sub>i</sub> is the score obtained by the study i; Σe<sub>i</sub> is the sum of the scores of all the studies). Once the WAs were estimated, the RRs were calculated between treatment groups and they were compared using 95% confidence intervals. The selected articles were extensively analyzed. When an article was not possible to get in a traditional way, contact with the authors was made electronically. This measure allowed for access to some studies that had not been possible to get. It was not possible to determine or assess the presence of potential publication biases.

An exploratory analysis of the data was carried out. Descriptive statistics were applied, with measures of central tendency (means and medians) and dispersion (extreme values). No sensitivity or subgroup analyses were applied. The study was funded with own funds and in collaboration with the master’s program in Medical Sciences at the Universidad de La Frontera.

Results

From the review of the various databases, we were able to verify that there were no related systematic reviews and the search made it possible to find a total of 3745 articles. Once analyzed by title, 112 studies were located (3.2%). By evaluating the abstracts of the titles identified, 41 articles were discarded for not adhering to the topic or not meeting the eligibility criteria, besides ruling out 5 for lack of abstract or article, leaving 66 items selected. Later, when assessing the abstracts, 13 were eliminated because they were duplicate studies, leaving 53 articles. Once critically read, 42 articles were eliminated for not meeting the study criteria, leaving 11 primary articles<sup>19-29</sup> that were rated by independent reviewers. They represent 0.3% of the initial total and 9.8% of the articles selected by title. Depending on the type of design of the selected articles, we were able to extract 13 series of patients, in relation to the therapeutic option performed, 9 series of ER and 4 RP, as shown in the flow diagram (Fig. 1).

The primary articles selected were published between 1997 and 2010, with a higher frequency of publications in 2008 (three articles). Regarding the type of design, 10 articles correspond to population registries of tumors and the remaining to a number of cases (Table 1). The 9 series of ER amount to a population of 244,147 subjects treated and the 4 RP series of 299,446, respectively.

Regarding the outcome variables, an article evaluates as outcome variable only the development of bladder cancer, three articles evaluate the development of rectal or colorectal cancer, and 7 consider other tumor sites including bladder, rectal, and lung. The results of the risk of occurrence of SPT are variable depending on the location. In assessing the characteristics of the populations studied, most articles do not record demographic data of the population, so it is only possible to collect the average age of the subgroups, finding an average age of 69.8 years for the series of patients undergoing ER and 67.9 years for RP.

The incidence in the time of SPT was 3.0% for the ER series (244,147 irradiated; 7361 with SPT), and 0.9% for the RP series (299,446 patients operated; 2735 with SPT). The median MQ in the series of irradiated patients was 15 points, with an average of 14.7 ± 1.1; and in the series of patients undergoing RP, the median MQ was 14 points, with an average of 14.3 ± 1.5. The WA of overall SPT (in all series) was 6.4%. The WA of SPT was 4.2% in the ER series and 2.2% in the RP series (p < 0.79).

In assessing the development time of SPT, it is observed that there is disparity in the articles. Some group the SPTs between 5 and 10 years after the initial treatment, and others beyond 10 years. Most articles do not provide data on the overall incidence of tumors, but only by location. This way, for the bladder location of second neoplasm, 5 ERs and one RP series were found, giving a WA of the RRs for bladder location of 0.96, and 0.8 for ER and RP, respectively, between 5 and 10. For more than 10 years of treatment, the WA of the RRs for second neoplasm of bladder location was 2.3 for ER and 0.8 for RP. For the rectal location of SPT, four series were obtained in the group of ER and one series in the RP group, which gave a WA of the RRs of 1.2 for ER and 0.7 for RP in the period of 5–10 years after treatment. For over 10 years, the WA of the RRs was 2.3 for ER and
Selected products
N=3745

Excluded by title
N=3633

Selected by title
N=112

Eliminated by eligibility criteria in the summary
N=41

Duplicates
N=13

Eliminated by eligibility criteria in the extensive
N=42

Selected for summary
N=66

Not found
N=5

Selected for the final analysis
N=11

Series to Study
N=13

Figure 1  Flowchart of the selection of the primary articles considered.

Table 1  Characteristics of the primary articles.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Database</th>
<th>Population under study (no. subjects)</th>
<th>Study period</th>
<th>Mean follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neugut et al.</td>
<td>1997</td>
<td>PBCR</td>
<td>141,761</td>
<td>1973-1990</td>
<td>8</td>
</tr>
<tr>
<td>Kendall et al.</td>
<td>2006</td>
<td>PBCR</td>
<td>273,773</td>
<td>1973-2001</td>
<td>5</td>
</tr>
<tr>
<td>Moon et al.</td>
<td>2006</td>
<td>PBCR and Medicare</td>
<td>140,767</td>
<td>1973-1999</td>
<td>10.6</td>
</tr>
<tr>
<td>Rapiti et al.</td>
<td>2008</td>
<td>Genova Cancer Registry</td>
<td>1134</td>
<td>1980-1998</td>
<td>7.4</td>
</tr>
<tr>
<td>Nieder et al.</td>
<td>2008</td>
<td>PBCR</td>
<td>243,082</td>
<td>1988-2003</td>
<td>4.1</td>
</tr>
<tr>
<td>Abdel-Wahab et al.</td>
<td>2008</td>
<td>PBCR</td>
<td>228,235</td>
<td>1973-2002</td>
<td>8</td>
</tr>
<tr>
<td>Bhojani et al.</td>
<td>2010</td>
<td>Quebec Cancer Registry</td>
<td>17,845</td>
<td>1983-2003</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not described; PBCR: Population Based Cancer Registry; PBCR-BC: Population Based Cancer Registry of British Columbia.

Table 2  Weighted average of standardized incidence according to the location of the new malignant tumors, with respect to time.

<table>
<thead>
<tr>
<th>Bladder location</th>
<th>Rectal location</th>
<th>Pulmonary location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series</td>
<td>WA SIR 5-10 years</td>
<td>WA SIR &gt;10 years</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

WA: weighted average; SIR: standardized incidence ratio.
0.55 for RP. In the pulmonary location group, we found two series of patients treated with ER and RP. Between 5 and 10 years after the treatment of the WA of the RRs, it was 1.4 for ER and 0.75 for RP; and for more than 10 years, 2.4 for ER and 0.7 for RP. These differences were not statistically significant in any of the comparisons (Table 2). In none of the articles reviewed did we find information regarding the secondary variables that we had decided to study (type and dose of radiotherapy).

**Discussion**

By conducting the analysis of the papers presented, we can see that they are all retrospective cohort studies, either compared with populations of patients with PC with another treatment or with cancer registries of the population adjusting for age and the follow-up time (Surveillance, Epidemiology and End Results [SEER] Program of the U.S. National Cancer Institute). This is understandable since there are no prospective individual works with such large casuistries that allow for a follow-up of more than 10 years, and the natural loss generated is a limitation at the time of evaluating the existing evidence. Moreover, as the comparison group is a population of the same biological and demographic characteristics, we are controlling potential biases such as genetic predisposition, the rigor of the health surveillance, and the characteristics of age, guaranteeing that the new malignancies are caused by radiotherapy and not by other associated factors.

Only 11 articles regarding the stated objective were found, because what was sought was to compare ER and RP. Many items were rejected for not reflecting the form of radiotherapy or the type of surgery performed; besides, many were included in the combination therapy groups, unable to separate them at the time of analysis, or new malignancies diagnosed within 5 years of the original treatment were included within the results.

When analyzing the methodological quality of the selected articles, the scarcity thereof stands out, since in most of them, the objectives are not indicated, and the sample size is not calculated or the inclusion or exclusion criteria are not satisfied, determining a low level of evidence. When applying the MINCIR methodological quality score (Table 3), no article achieved the minimum score for consideration of an acceptable quality.

When comparing the weighted incidence of new malignancies in patients undergoing RP versus those undergoing ER, we can see that there is twice the risk of presenting a new malignancy in patients undergoing ER, but the low number of works and the low incidence of the tumors did not make it possible to establish a statistically significant difference. Besides, we must consider that the incidence is determined by the size of the population, and it decreases dramatically over the years, so the incidence of new malignancies increases artificially.

When assessing the location of the second tumors, we can see that in general there is an increase of these in the areas adjacent to the area of irradiation; that is, bladder and rectal. Within the new malignant tumors of extra-pelvic location, the most frequent was lung cancer, assessed in 4 of the articles; three others assessed all the tumor sites present in the patients with PC and found no significant differences in most of them. The reason why there is a significant increase in lung tumors is uncertain, but it could be related to environmental factors such as smoking.

In order to assess the time of development of new malignancies, it was necessary to associate it to the most common locations thereof, which lead to compare smaller series of patients and found greater differences between the groups, increasing the risk for patients with radiotherapy; but the results must be considered with caution, because it is a small sample. On the other hand, the results being expressed as standardized incidence and having weighted the methodological quality of the studies, this makes them more comparable. We were unable to assess the relation between radiotherapy dose and incidence of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>MINCIR methodological quality score.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Domain</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>1. Study design</td>
<td></td>
</tr>
<tr>
<td>Multicenter clinical trial</td>
<td>12</td>
</tr>
<tr>
<td>Double-blind randomized controlled clinical trial</td>
<td>9</td>
</tr>
<tr>
<td>Clinical trial (not blinded or simple, not randomized)</td>
<td>6</td>
</tr>
<tr>
<td>Concurrent or prospective cohort</td>
<td>4</td>
</tr>
<tr>
<td>Historical or retrospective cohort</td>
<td>3</td>
</tr>
<tr>
<td>Cross-sectional cut</td>
<td>3</td>
</tr>
<tr>
<td>Series of cases</td>
<td>1</td>
</tr>
<tr>
<td>2. Study population x factor of justification (FJ = 2 justifies the sample and 1 does not justify)</td>
<td></td>
</tr>
<tr>
<td>&gt;201</td>
<td>6–12</td>
</tr>
<tr>
<td>151–200</td>
<td>5–10</td>
</tr>
<tr>
<td>101–150</td>
<td>4–8</td>
</tr>
<tr>
<td>61–100</td>
<td>3–6</td>
</tr>
<tr>
<td>31–60</td>
<td>2–4</td>
</tr>
<tr>
<td>&lt;30</td>
<td>1–2</td>
</tr>
<tr>
<td>3. Methodology used</td>
<td></td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td></td>
</tr>
<tr>
<td>The design employed is mentioned and justified</td>
<td>3</td>
</tr>
<tr>
<td>The design employed is mentioned</td>
<td>2</td>
</tr>
<tr>
<td>The design employed is not mentioned or justified</td>
<td>1</td>
</tr>
<tr>
<td><strong>Criteria for selection of the sample</strong></td>
<td></td>
</tr>
<tr>
<td>The inclusion and exclusion criteria are described</td>
<td>3</td>
</tr>
<tr>
<td>The inclusion or exclusion criteria are described</td>
<td>2</td>
</tr>
<tr>
<td>The selection criteria are not described</td>
<td>1</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td>It justifies the sample used</td>
<td>3</td>
</tr>
<tr>
<td>It does not justify the simple used</td>
<td>1</td>
</tr>
<tr>
<td><strong>Final score</strong></td>
<td></td>
</tr>
<tr>
<td>Domain 1 + (domain 2 x justification factor) x domain 3</td>
<td>6–36</td>
</tr>
</tbody>
</table>

a It includes clinical trials with restricted randomization and nearly experimental studies.

b It includes experimental studies (before and after).
newmalignancies. Information on the type of radiotherapy used was not obtained either.

The works are based on data from population registries of tumors in 10 of the articles, which determines significant biases, since these records only have general data of the patients. In addition, the records come from very diverse time periods, as an important part is from the pre-PSA era, which determines probably more advanced stages in the records before the 90s. The articles, due to the unavailability of the total population in the different periods of time, base their study on determining the risk of a new malignancy compared with the records of patients with cancer or a control group, thus, expressing their results as a ratio between the observed tumors divided by the expected ones, to what is called either relative risk (RR), hazard ratio (HR), or standardized incidence ratio (SIR), values that could only be compared partially for the locations of most frequent tumors in relation to the periods of time most used.

The main limitations of the study are mainly due to the quality of the primary studies, generally of low level of evidence (level 4 for damage and therapy scenarios34) and MQ (between 13 and 16 points36). Scarce data were also provided and this situation complicated the comparison and the subgroup analysis.

In conclusion, we can consider that the information available today does not reveal a statistically significant increase in the risk of development of SPT associated with some of the treatments assessed; however, we must consider that there is a clear trend to the development of second neoplasm in the group of irradiated patients. Moreover, it is clear that the poor MQ of primary studies complicates the interpretation of results even more. There is clearly a need for future prospective and multicenter studies that help clarify the true risk of second malignancy after the different therapeutic modalities of prostate cancer.

Conflict of interest

The authors declare that they have no conflict of interest.

References


