Complications and nerve preservation in prostatectomy according to the time interval from diagnostic biopsy

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Abstract

Objectives: To summarize the available evidence on complications and bilateral nerve preservation in radical prostatectomy (RP) in patients according to the time interval from diagnostic biopsy (more or less than 6 weeks).

Materials and methods: Relevant studies were identified by using structured and specific search strategies for each of the databases consulted, without limitations. The methodological quality of each of the studies included was evaluated and the data were extracted independently.

Results: For open RP, two of the studies concluded that a time interval of less than 4 or 6 weeks between prostate biopsy and surgery had no influence on the postsurgical complications rate or on nerve preservation during surgery. For laparoscopic robotic-assisted RP, the study included concluded that performing this type of intervention in an interval of less than 4 or 6 weeks after diagnostic biopsy was associated with a higher risk of postsurgical complications. However, all these studies had major methodological limitations.

Conclusions: The time interval between diagnostic biopsy and open surgery has no influence on the complications rate or nerve preservations. In contrast, an interval of less than 4 weeks between diagnostic biopsy and laparoscopic surgery is associated with a higher risk of surgical complications.

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KEYWORDS
Intraoperative complications; Prostatectomy; Prostate neoplasms; Biopsy
Introduction

Prostate carcinoma is the most common male urogenital cancer and it is the third cause of death in the European Union, reaching a mortality rate of 13.9 per 100,000 in 2001. In 2007, prostate cancer meant the death of about 5574 Spanish men at a mean age of 75.17 years. Radical prostatectomy (RP) is an effective option to treat localized prostate cancer, as for the perioperative morbidity and mortality rates, and the profile of side effects and cancer control rates achieved, both long-term. The surgical options available for the performance of RP are primarily: open (retropubic or perineal) and laparoscopic (simple and robot-assisted) RP.

However, none of these techniques is free of the complications inherent to their use. The most frequent postoperative complications resulting from prostatectomy are urinary incontinence and impotence, both produced by surgical damage to the urinary sphincter and surrounding neural structures. Their appearance is determined by the experience and level of knowledge of the surgeon who performs the procedure.

Although these postoperative complications are well known and documented enough, there is controversy over whether their incidence is related and to what extent to the amount of time from the performance of the diagnostic biopsy of prostate cancer to the completion of the RP. The recommendation to wait for a time longer than or equal to 4–6 weeks after transrectal prostate biopsy to perform the open RP is now widely accepted, because in this way, a reduction of periprostatic inflammation and complete resolution of the hematoma secondary to biopsy are possible. However, other authors support the idea that carrying out the RP shortly after the biopsy can increase the difficulty to dissect the surgical planes and the rate of complications, although this claim is not sufficiently proven. Imaging studies such as endorectal MRI, performed after the completion of a diagnostic prostate biopsy, suggest that the changes persist and are not fully resolved until 21 days later, and, in some cases, up to 4.5 months.

Nevertheless, and despite the implications that this association might have for the prognosis of future patients who will undergo RP, there is an important lack of specific studies to assess the minimum time interval between the diagnostic biopsy and the RP to improve the resolution of the complications of the biopsy (including the preservation of neural structures) and to achieve optimal patient recovery after surgery. Therefore, and in the absence of explicit evidence on the relation between the rate of postoperative complications and bilateral nerve-sparing capacity (BNSC) of the RP and the time interval between diagnostic biopsy and surgery, this study aims to find and synthesize the available evidence on the matter.

Objective

To synthesize the available evidence on the rate of complications and BNSC of the RP in terms of the time from the ultrasound-guided diagnostic biopsy (shorter versus longer than 6 weeks) in patients diagnosed with prostate cancer.

Evidence acquisition

By using a structured search strategy according to the Population, Intervention, Comparison, and Outcomes (PICO) format, the identification of relevant studies related to the...
rate of complications and BNSC of the RP was carried out depending on whether it was performed before or after the 6 weeks of the diagnostic biopsy of prostate cancer.

The search strategies developed were specific for each of the databases searched: Medline (including PRE-MEDLINE via PubMed), Embase (Evidence Based Medicine), and the Cochrane Library as shown in Table 1. Open strategies with free text were also used to search studies in other databases and cross reference lists of all relevant articles were revised.

The search was conducted without any limitation by date, language, or type of study, and it included all the studies related to the topic and published until May 2010.

The assessment of the inclusion of the studies identified in the search was based on the following criteria:

- **Type of studies.** Any type of study which analyzed the issue in question with the exception of letters to the editor or conference proceedings.
- **Type of participants.** Adult male patients diagnosed with prostate cancer confirmed by ultrasound-guided prostate biopsy and subsidiary of RP. We excluded pediatric patients and patients diagnosed with prostate cancer not subsidiary of RP.
- **Type of intervention.** RP, practiced in any of its forms available, open (retropubic or perineal) or laparoscopic (simple or robot-assisted).
- **Outcome measures.** The main outcome measures were the rate of postoperative complications (represented by the estimated blood loss (EBL), the number of transfused packed red blood cells, major complications, urinary continence, erectile dysfunction, and other complications) and BNSC.

One author conducted a revision of titles and abstracts of all of them to establish whether these studies met the inclusion criteria agreed or not. The studies that met these criteria were evaluated to establish their validity and extract their data. This review was subsequently subjected to a second assessment by a reviewer.

In order to assess the methodological quality of the studies included, we proceeded to make a critical reading by identifying the presence of possible biases and methodological weaknesses that could influence the interpretation and validity of the results. To do this, we used a methodological tool,9 designed to assess cohort, case and control, and cross-sectional studies, which analyzes the performance of 6 items related to the study design, study sample, the quality of the outcome measure, the follow-up of the patients, or the potential confounding factors that may have influenced the obtention of results.

The following data were then extracted independently using data extraction forms appropriate to the subject under study, and with these data, we constructed evidence tables where the main characteristics of the included studies were synthesized.

### Evidence synthesis

As described in Fig. 1, a total of 50 records were obtained by the search described, related to the subject under study. Of these 50 records, 43 were excluded by the title, keywords, and abstract. None was doubled and the reason for their exclusion was the lack of compliance with some of the established requirements for assessment, such as the age of the participants (pediatric) or the absence of analysis of the subject matter. Of the 7 remaining records selected for critical reading, 4 did not assess outcome variables related to postoperative complications or the BNSC of the prostatectomy, so they were excluded. The studies rejected at this stage were the one by Boorjan et al.14 for not analyzing complications arising from the implementation of RP or showing results related to BNSC, the one

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Search strategies in Medline, Embase, and Cochrane.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy</strong></td>
<td><strong>Embase</strong></td>
</tr>
<tr>
<td>(interval and biopsy and prostatectomy and (outcome* or recurrence or perioperative or postoperative or complication* or adverse)).m_title.</td>
<td>interval:ti and biopsy:ti and prostatectomy:ti and (outcome*:ti or recurrence:ti or perioperative:ti or postoperative:ti or complication*:ti or adverse:ti)</td>
</tr>
<tr>
<td>biopsy, fine-needle/ or biopsy/ or biopsy, needle/ prostatectomy/ prostatic neoplasms/su [surgery] time factors/ ('&quot;6&quot; adj1 week*).mp. [mp = title, original title, abstract, name of substance word, subject heading word, unique identifier] intraoperative complications/ postoperative complications/ treatment outcome/ neoplasm recurrence, local/ 2 and (3 or 4) and (5 or 6) and (7 or 8 or 9 or 10) from 11 keep 1, 18, 26–27, 30–31, 36, 47 1 or 12</td>
<td>'prostate biopsy'/exp and 'prostatectomy'/exp '6 weeks':ab,ti or '4 weeks':ab,ti #2 and #3</td>
</tr>
<tr>
<td></td>
<td>'therapy delay'/exp #2 and (#3 or #5) #1 or #6</td>
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<td></td>
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<td></td>
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</tbody>
</table>
Conducted by Shibata et al.\textsuperscript{15} for using the effect on PSA* and the risk of recurrence as an outcome measure, but not the complications of the surgical intervention, the one conducted by Vickers et al.\textsuperscript{16} for using surrogate type outcome variables, and the one by Van Den Bergh\textsuperscript{17} because the inclusion of the study population was based on PSA levels and not the diagnosis of prostate cancer.

Therefore, we considered the final inclusion in this review of 3 studies, all observational, descriptive, cross-sectional studies.

The three studies included were subjected to critical reading in order to identify the presence of possible biases and methodological flaws that limited the validity of the results obtained. By using a methodological tool for evaluating cohort, case and control, and transversal studies,\textsuperscript{4} 6 parameters were evaluated in relation to the design used, the study population, the quality of the outcome measure, the follow-up of the patients or potential confounding factors that might have influenced the results obtained.

Thus, in general, a moderate-low methodological quality of the articles included was observed, the type of study design, quality control, changes in time (different tumor stages), and the possible presence of confounding factors being the methodological issues identified as most deficient. In all of them, valid and reproducible outcome measures were used, and sample sizes that ensured sufficient statistical power to detect significant differences were often used (except for one,\textsuperscript{9} in which the sample was scarce compared to the rest). Although, because we want to know the effect of a treatment, the most appropriate type of design is the clinical trial, all the studies included used cross-sectional study designs. The total score obtained and the deficiencies found according to these criteria for each clinical trial are presented below in Table 2.

In total, 3724 men diagnosed with prostate cancer using ultrasound-guided prostate biopsy who underwent RP were analyzed retrospectively using medical records or specific databases. The mean age of the participants was 62 years, and they were treated at the urology departments of universities or national institutes of health located in the U.S. The time interval in which these surgeries were performed was between 1986 and 2007, and the intervention techniques used were retropubic RP\textsuperscript{9,10} and robot-assisted laparoscopic RP.\textsuperscript{11} In one of them,\textsuperscript{10} bilateral pelvic lymphadenectomy was also a necessary requirement, as well as attempted treatment before performing surgery. Among the most common exclusion criteria, there were history of grafting of the sural nerve, hernioplasty, and neoadjuvant androgen ablation.

In all the studies included, the BNSC and the rate of complications of the RP were analyzed by means of different outcome variables recorded in medical records or databases of medical institutions. Also, they all established two cut-off points for the time interval from the prostate biopsy to the prostatectomy (4–6 weeks) in order to compare the results obtained before and after these limits.

Thus, the study conducted by Lee et al.\textsuperscript{9} in 2006 was performed in order to determine if the time interval between the prostate biopsy and the RP had any effect on the outcomes of the immediate postoperative period and, as a secondary objective, to determine the minimum time period necessary to allow for the performance of the RP without compromising the results. To do this, they included a total of 169 patients who had undergone open RP for prostate cancer in years 2001–2004 and whose diagnosis had been established by ultrasound-guided prostate or transrectal biopsy before the intervention. All the patients included were from the Department of Urology at the University of Iowa, in
Table 2  Assessment of the methodological quality of the studies included.

<table>
<thead>
<tr>
<th>Question</th>
<th>Quality parameters</th>
<th>Lee et al.⁹</th>
<th>Eggener et al.¹⁰</th>
<th>Martin et al.¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Is the study design appropriate for its objectives?</td>
<td>Treatment</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Controlled trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Is the study sample significant?</td>
<td>Origin</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Inclusion and exclusion criteria</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(3) Is the control group acceptable?</td>
<td>Validity</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) Are the measures and the results high quality?</td>
<td>Reproducibility</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Quality control</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>(5) Was the follow-up complete?</td>
<td>Unusual treatments</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>(6) Are there confounding factors?</td>
<td>Changes in time</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Confounding factors</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Reduced distortion by</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>means of the analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

++ = significant deficiency; + = minor deficiency; 0 = there are no deficiencies; NA = not applicable.

the United States, and they had been followed up with, at least, three visits after the intervention (every month, every 3 months, and every 6 months). Men with a history of sural nerve grafts or other surgical interventions such as hernioplasties were not included. From the data recorded in medical records, the following variables, among others, were collected: patient’s age, time of diagnosis, and time interval between the biopsy and the RP, and after the intervention: estimated blood loss during the intervention, nerve sparing rate, number of transfused packed red blood cells, major complications, and urinary continence. An analysis adjusted for potential confounding factors and using a definition of statistical significance of $p < 0.05$. The mean age of the study population was 59 years (45–72) and the mean time interval between the diagnostic biopsy and the prostatectomy was 70.05 days (14–378) with a median of 56 days. The predominant tumor stage was T2b (70%). 25% underwent RP for prostate cancer before the 6 weeks and 5.3% before the 4 weeks, both time intervals after the diagnostic biopsy. No participant underwent prostatectomy in a time interval shorter than 2 weeks. Complications occurred in 8% of the patients and they consisted of pelvic bruising, clot retention, lymphocele formation, or need for transfer to respiratory and heart intensive care units. There were no deaths and 80% of the study participants fully recovered from urinary incontinence secondary to the intervention. There were no significant differences in the estimated blood loss during the intervention, the nerve complication rate, the rate of blood transfusions performed, major complications, or postsurgical urinary continence in patients with time intervals between the diagnostic biopsy and the RP higher and lower than the median. No direct or indirect correlations between the time interval between the diagnostic biopsy and the RP and any other outcome considered in the study were found either. Among the limitations of the study, we can highlight the type of design used (retrospective and observational), a small number of study population, and the failure to obtain all the biopsies by the same institution, which could have meant some variability in the technique of data collection. This study concluded that the time interval between the prostate biopsy and the retropubic RP appears not to influence the immediate postoperative complications, not being possible to determine the minimum time period required to perform the prostatectomy without increasing the complication rate beyond 2 weeks.

In 2007, the group of Eggener et al.¹⁰ analyzed using a cross-sectional study whether the RP performed before or after the 4–6 weeks after the prostate biopsy is associated to the efficacy or the difficulty of the surgical intervention. The study population consisted of 2996 patients diagnosed with localized prostate cancer who underwent retropubic RP and bilateral pelvic lymphadenectomy between 1986 and 2004, from the Department of Urology of the National Institute of Health in New York. The patients with a personal history of neoadjuvant androgen ablation and RP for failure of the implementation of previous radiotherapy were excluded from the study. From a clinical database constituted by the data collected by the surgeons in charge of carrying out the surgical interventions, the following outcome variables were collected: the mean estimated blood loss during the surgery, the bilateral nerve damage, the
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erectile function, and the degree of urinary continence. In 6% of the patients, the time interval between the diagnostic biopsy and the RP was equal to or shorter than 4 weeks, and in 14%, not exceeding 6 weeks. The patients with an interval shorter than or equal to 6 weeks had worse clinical stage (T2 or more 56% versus 49%, p = 0.01). Univariate analysis showed that a short time interval between the biopsy and the RP was associated with a significant reduction in the probability of bilateral nerve injury, although there were no significant differences in terms of erectile dysfunction two years after the intervention.

A multivariate analysis in which the surgeon’s experience and several features of the disease were controlled found no significant differences in the association of the time interval of 4–6 weeks with the estimated blood loss (for both p = 0.09), with the erectile function after two years (p = 0.4 and p = 0.6, respectively), or with the urinary incontinence after two years (p = 0.18 and p = 0.9, respectively). As limitations of the study, the type of study design used (retrospective and observational), the use of strict and little generalizable inclusion criteria of the study population, and certain deficiencies in the quality control of the outcome measure can be highlighted. The study concludes that the open RP performed within a short period of time, before the 4 or 6 weeks after the prostate biopsy, does not appear to increase the technical difficulty of the surgical intervention or affect the urinary continence or erectile function of the patient with prostate cancer, so there is no reason to delay the performance of the surgery after the prostate biopsy.

In 2009, Martin et al. conducted a cross-sectional design study in the United States in order to determine whether short intervals (shorter than 4 or 6 weeks) between the prostate biopsy and the Robot-Assisted Laparoscopic Radical Prostatectomy (RALRP) have a detrimental effect on the results obtained in the perioperative period. The study population was made up of 559 patients diagnosed with prostate cancer who had undergone RALRP for a period of time between 2004 and 2007 and whose diagnosis had been determined by ultrasound-guided biopsy. The origin of the participants in the study was not specified, and those patients who underwent RALRP before 2004 were excluded. A comparison between subgroups that were formed by the patients who had undergone RALRP before and after the 4 and 6 weeks of the diagnostic biopsy was carried out. From the database of a department of urology, different outcome variables were recorded, among them, the use of nerve sparing techniques, the estimated blood loss during the surgery, the rate of transfusions performed, and the complications that occurred while performing the surgery. The subgroups established proved to be homogeneous in terms of the preoperative variables measured. In the group that had undergone RP before the 4 weeks of the prostate biopsy, significant differences in terms of the overall complication rate (p = 0.04) were found compared with the subgroup in which the surgery was performed after the 4 weeks (18.5% vs 6.9%). In the subgroup of patients undergoing surgery in a period of time shorter than 6 weeks of the diagnostic biopsy, there were significant differences, although very small in terms of the overall complication rate (p = 0.03) compared with the subgroup of patients operated after the 6 weeks of the diagnostic biopsy (13.6% vs. 6.4%). A multivariate analysis in which confounding factors such as patient’s age, Gleason score, size of the lesion, and number of biopsies were controlled showed in a statistically significant way that the patients in the intervention subgroup prior to the 6 weeks of the prostate biopsy were more likely to be transfused (p = 0.01). Those complications less likely to be related to the difficulty in the dissection of surgical planes, such as ST elevation, deep vein thrombosis, acute renal failure, or wound infection occurred in the groups that were operated on later (after the 4 and 6 weeks following the prostate diagnostic biopsy). The limitations of the study are directly related to the type of design used for the performance of the study and the heterogeneity in the size of the subgroups established, with a majority participation in the study of patients with late interventions (after the 4–6 weeks of the prostate biopsy). In conclusion, the study states that the RALRP should be delayed between 4 and 6 weeks after the diagnostic prostate biopsy as this time interval is associated with an increased risk of complications, even when the relevant characteristics of the patient and prostate cancer are considered.

Discussion

The data obtained show that the time interval between the diagnostic prostate biopsy and the open RP does not seem to affect the immediate postoperative results with regard to intraoperative bleeding, postoperative erectile dysfunction, or urinary incontinence. Moreover, according to the studies included, a time interval shorter than or equal to 4 or 6 weeks does not increase the surgical difficulty or decrease the ability of the physician to achieve the desired results. Therefore, the results show that the current recommendation to wait for the completion of the surgery 6 weeks after the biopsy might not be necessary in all the patients to ensure a reduction in postoperative complications.

However, one of the studies included showed that a shorter time interval between the performance of the diagnostic biopsy and the RP could indeed be associated to a greater estimated blood loss during the intervention. This can be attributed to an incompletely resolved local inflammation or a major difficulty when dissecting the surgical tissue planes, although this needs to be studied further in prospective studies to be confirmed.

These results agree with those obtained by other studies included in conference proceedings, and that, due to the limited inferential power of this type of design, they could not be included in this work, like the one conducted by Tå, with the objective of evaluating if the time interval between the prostate biopsy and the total prostatectomy has any impact on the surgical outcomes. The study concluded that the total prostatectomy can be safely performed within the 6 weeks after the prostate biopsy without implying an increase in postoperative complications, although the performance of this surgery before the 6 weeks significantly reduces the surgeon’s ability to perform nerve-sparing techniques during the intervention.

With regard to robot-assisted laparoscopic radical prostatectomy (RALRP), statistically significant differences were found between a higher rate of complications in study groups undergoing early RP from the performance of the prostate biopsy compared to the study groups in which the
intervention was performed later, even after performing a multivariate analysis considering other related variables. The discrepancy found in the results obtained by the open RP, in which this type of association has not been found, and the one performed laparoscopically may be due to a less invasive nature than that of the RALRP. The low estimates of blood loss during surgery and the rate of major complications in the study of this type of technique compared to those that occur with open RP might reveal certain confounding factors masked as the time interval between the diagnostic biopsy and the prostatectomy, which still play an important role in perioperative morbidity. That is, inflammation and an increased difficulty to distinguish the surgical planes between the rectum and the prostate by the surgeon could be a minor complication while performing open RP compared to other techniques such as RALRP. Usually, the visualization of the surgical field in three dimensions compensates for the absence of physical contact of the surgeon with that field. However, the inflammation and destruction of surgical planes after the performance of the diagnostic prostate biopsy can lead to a decreased visualization of the field with a likely increase in blood loss, which may negatively influence the appearance of perioperative complications.

Similar results were obtained by Choi when, in 2009, he analyzed the possible relation between intraoperative bleeding and various time intervals between the biopsy and the robotic-assisted laparoscopic prostatectomy, based on the experience of a single surgeon. This study concludes that this type of surgery should be performed after the 4 weeks of the diagnostic prostate biopsy.13

However, besides the type of surgical intervention, other factors inherent to the performance of open surgery that could affect the rate of postoperative complications more than the time interval between the prostate biopsy and the RP and which may have an influence as confounding factors on the results obtained have been described. These factors include the size of the surgical incision or the amount of blood lost during the intervention, as well as the prostate size. However, these factors have not always been considered by the studies included in this review.

Among the main limitations of the included studies are the use of a small study population as well as the existence of important disparities in the number of participants in each study group which may have influenced the statistical analysis of complications such as transfusion rates. In addition, the study design used, cross-sectional, does not make it possible to establish a real association between variables beyond the mere information on the apparent association between the risk factor and the disease. Regarding the surgical techniques studied by the works included, there is a degree of heterogeneity, because while two of the studies used patients who had undergone open PR, one studied patients undergoing robot-assisted laparoscopic surgery. This has the added difficulty of knowing the degree of application of these results to other surgical techniques performed perineally or carried out by means of non-robot-assisted laparoscopy. In one of the studies included, the diagnostic biopsies were not taken at the same institution, which could lead to certain differences in the techniques of collection or in the processing of the sample that may have influenced the results obtained. Moreover, in none of the studies is the method used to measure the outcome variables detailed, such as the estimate blood loss, urinary incontinence, or nerve preservation, which, together with the fact that the patients included in the studies suffered from various evolutionary stages of prostate cancer, and that the quality of the studies included is moderate-low, clearly limits the validity of the results.

Conflict of interest

The authors declare that they have no conflict of interest.

References


