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Editorial

Critical review of use of radiation as initial treatment for localized prostate cancer

Revisión crítica del uso de radiación como tratamiento inicial del cáncer de próstata localizado

The current profile of patients with prostate cancer (PCa) corresponds to a still "young" patient with a long life expectancy, sexually active, and with no prior relevant voiding problems. More than 75% of PCa cases are currently diagnosed at a localized stage[1]. The main goal in patients with localized PCa will be to perform a treatment that provides the greatest cure rate with the least functional morbidity (urinary continence and sexual potency), but if initial treatment fails and salvage therapy is required, the second priority should be to continue to attempt cure with a minimum functional impairment.

According to multiple studies, the most widely used and effective treatments are radical prostatectomy (RP) and radiotherapy (RT), either as external radiotherapy or brachytherapy[1]. Although these therapies are considered to provide similar results, there is currently no prospective, randomized study comparing both approaches. A recent review study based on the CAPSURE (Cancer Prostate Strategic - Urological Research Endeavor) reported failure of initial treatment in approximately 30% of men with PCa. Of these, 63% had undergone RT and only 23% RP[2]. A detailed analysis demonstrated that 19% of patients undergoing RP and 45% of those receiving RT had high-risk tumors, while both treatment groups were very similar in all other parameters[2]. Regardless of the results of this study, and although none of these treatments has been shown to date to be superior to the other in terms of cure rate, a debate as to what is the best treatment may be opened based on various details related to effectiveness, follow-up, morbidity, and salvage options when treatment for localized PCa fails. For this, some recently published studies which question the assumed equivalence of surgery and radiotherapy have been selected.

Oncological control

Oncological control of patients undergoing RT for localized PCa consists of measurement of plasma levels of prostate-specific antigen (PSA)[1]. Criteria for defining biochemical recurrence after RT have gradually changed in recent years, searching for an objective standard which has not been achieved yet. The first definition was established in 1996 by the consensus panel of ASTRO (American Society Therapeutic Radiology and Oncology) as three consecutive PSA elevations from its nadir[3]. Experience showed that this definition was dependent on follow-up frequency and duration and was substantially artifacted. For this reason, another ASTRO consensus panel redefined biochemical recurrence in 2005 as the numerical cut-off point obtained by adding a PSA value of 2 ng/mL to the nadir, measured after RT[4]. This is the currently valid criterion.

On the other hand, the outcome of RP depends only on complete removal of the prostate gland, and monitoring is focused on the search for an undetectable PSA. From the beginning of the technique, the different urological associations agreed that two consecutive elevations with a PSA level of 0.2 ng/mL according to the European Association of Urology (EAU) or > 0.4 ng/mL according to the American Urological Association (AUA) represented the standard definition of biochemical relapse after RP. Because of the absence of prostatic tissue, use of PSA after RP is a highly sensitive tool for detecting treatment failure.

By contrast, the ASTRO criterion shows the difficulty of oncological control after RT using PSA, due to the prolonged and unpredictable therapeutic effect of radiation and to the persistence of functioning residual prostatic tissue producing PSA. These circumstances and

the different procedures used for measuring outcomes involve inevitable bias and methodological limitations when studies comparing oncological control rates after RP and RT are conducted.

A recent study by Walsh et al[5] analyzed which would be the oncological results of RP if a criterion equivalent to that currently accepted by ASTRO was applied.

The study reported that biochemical relapse-free survival would be overestimated, recurrence detection would be delayed, and mean recurrence-free time would increase (virtually three times). It would therefore not appear adequate to compare oncological control rates after RP and RT for localized PCa using the current criteria for post-RT recurrence. Moreover, another recent study confirms the limitations of PSA for monitoring PCa treated with RT[6]. This study analyzed 21 patients treated with RT for PCa who underwent during follow-up radical cystoprostatectomy (RCP) for reasons not related to their prostate tumor, an infiltrating bladder cancer in most cases (19). Seventeen patients had been treated for PCa with external RT, and 4 with brachytherapy. Only 18 of the 21 patients had an evaluable post-RT control PSA at follow-up; of these, 16 (89%) met the 2005 ASTRO criteria for freedom of biochemical recurrence. However, pathological analysis of the RPC specimens showed residual PCa in 52% (11 out of 21 patients), i.e. more than half the patients assumed to free of recurrence based on the 2005 ASTRO criteria for PSA had residual PCa. It is well known that the curative effect of RT on PCa may be delayed for up to 12-18 months. This is the reason why prostate biopsies are not recommended until 24-36 months after RT, in order to avoid false positive results[7]. This study reported a mean time from RT to RPC of 60 months, sufficient for RT to have exerted its whole therapeutic effect[8], demonstrating the limitations of PSA for monitoring PCa treated by RT, as well as the difficulties of RT to achieve immediate or definitive control of disease. In addition, adjuvant therapies, such as hormonal blockade, which continue to be usually associated to RT condition patient's quality of life, increase treatment costs and, above all, make assessment of results even more difficult. In contrast to these disadvantages, assessment of results after RP is simple and objective, which makes it possible to take immediate therapeutic measures if persistent or recurrent disease is detected.

Functional outcome

In patients undergoing RP in whom residual disease or local biochemical failure is detected, RT may be used as a salvage procedure. Salvage therapies should be aimed at achieving the same goal as initial therapy: to optimize oncological and functional outcome. Oncological follow-up after a salvage therapy with either RT or RP provides similar oncological results[8]. However, from the functional viewpoint, urinary, sexual, and gastrointestinal morbidity is very different depending on the initial and salvage therapies used. While RT is a resource easily applied after RP, achievement of satisfactory results for the patient is much more difficult when the sequence is the opposite (surgery after a prior RT). Studies analyzing use of adjuvant or salvage RT after RP have reported higher rates of sexual and rectal adverse effects, but no impairments of the continence status after RP[8], even following salvage with high RT doses (70 Gy)[9]. When RT is the initial therapy and a salvage RP is decided, morbidity greatly increases even in experienced hands, with incontinence rates higher than 50%[10]. Risk of cervical sclerosis and complete loss of sexual potency in patients who still have it also increases[11]. There is also an increased risk of rectal lesion during RP in the irradiated territory, which will probably sentence the patient to a permanent colostomy. Even when laparoscopic or robotic approaches are used in cases where they are technically feasible, a greater morbidity is seen[12]. The problem mainly occurs in healthy patients with a long life expectancy, in whom salvage RP would severely increase morbidity and all other local salvage alternatives available (cryotherapy, HIFU [high intensity focused ultrasound]) have no adequate follow-up or scientific evidence to be recommended and may cause a significant morbidity when used as post-RT salvage therapies. As a result, our "young" patient with localized PCa treated by RT and local recurrence will only have available a palliative treatment, such as lifetime hormonal blockade, which even if given using an intermittent scheme will be associated to mid and long-term adverse effects[13]. Moreover, if incontinence and/or impotence occurs after treatment for a localized PCa, placement of an artificial sphincter and/or penile prosthesis will be more feasible in an area which has only undergone surgery as compared to an irradiated area, where subsequent surgery is highly complex and has less chance of success.

Adverse effects and complications

Occurrence of second malignancies, which tend to involve the bladder, in patients treated for PCa is another issue of interest[14]. The factor most commonly related to such conditions include smoking and prior RT to the pelvic area[14,15]. Patients who undergo RT for PCa have an even greater risk of developing a second cancer, both in the pelvis and in areas close to the irradiated field[16]. Studies on large populations show that prostatic RT is significantly associated to an increased risk of developing a second tumor, particularly in patients with a long survival[17,18]. Such greater risk becomes evident over time, and 34% of patients experience such tumors more than 10 years after irradiation.[17] The most common sites are the bladder and rectum, but distant organs are also involved, even when IMRT (intensity-modulated radiotherapy) is used[18]. These second malignancies are usually of a higher grade and with more aggressive histological patterns[19]. Second tumors have also been reported after brachytherapy[20]. Patients with localized PCa and a long life expectancy will be most affected by this risk of second malignancies after RT. By contrast, there is no study showing any relationship between treatment of PCa by RP and occurrence of second malignancies.

The therapeutic scheme of external RT is currently evolving towards use of conformational radiotherapy and IMRT. This modality encompasses more fields and uses higher doses in the tumor area, exposing greater volumes of normal tissue to low radiation doses. Both conformational RT and IMRT also involve the abovementioned increased risk of second tumors and a greater risk of severe complications which, while uncommon (radiation-induced bladder disease and proctitis, ureteral entrapment, dermatitis), will sometimes require aggressive measures such as palliative cystectomy or intestinal diversion[21].

Open RP has been associated since its description to morbidity related to continence and potency, but in recent years advances in understanding of prostatic anatomy, as well as spectacular progress in surgery thanks to laparoscopy and robotics, have allowed for achieving excellent oncological and functional results[22]. In addition, blood losses during surgery are minimal, and hospital stay and catheterization times are short. The most recent results reported for laparoscopic and robotic RP refute the traditional argument that RT has advantages in terms of continence and potency, and also avoids the disadvantages of surgery (surgical wound, bladder catheter)[22].

Conclusion

All previous considerations should lead urologists and radiotherapists to critically reflect on the indication for use of RT as initial treatment for localized PCa. Based on the above arguments, RP should be considered as the only initial choice for treating localized PCa in the frequently found "young" patients with a long life expectancy, sexually active, and with no voiding disorders. Patients who are initially offered to choose between RP and RT should be given realistic information about the efficacy and outcome of both procedures, the follow-up modality, short and long-term adverse effects, and the options for salvage if one or the other therapy fails.

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