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May intra-operative radiotherapy have a role in the treatment of prostate cancer?

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Abstract

Treatment of locally advanced prostate cancer is still a challenge. Combined treatments including hormone therapy, radiotherapy, and/or surgery can achieve less than 50% of disease free survival at 10 years. Almost 50% of patients with locally advanced disease after radical prostatectomy experience local relapse and biochemical failure occurs up to 70% of cases after radiotherapy and hormone therapy. Postoperative radiotherapy has recently demonstrated to improve biochemical and clinical outcome in pT3 and/or positive margin tumors in 3 large randomized trials. Therefore, combining surgery and intra-operative radiotherapy (IORT) might be of value in this patient population. Recently, a number of studies have shown the feasibility of IORT, delivered with dedicated linear accelerators, combined or not with external beam radiotherapy with the aim of improving clinical outcome and possibly shortening overall treatment time. Preliminary clinical results look encouraging and could be the premise for future controlled prospective phase III trials.

Keywords: Intraoperative radiotherapy; Surgery; Prostate cancer

1. Introduction

The optimal treatment of prostate cancer is still a controversial issue. Although low risk prostate cancer has a relatively favorable prognosis with disease-free survival rates of 80–92% at 5 years and of 76–92% at 10 years either after radical prostatectomy or curative radiotherapy, intermediate and even more high risk patients have less satisfactory outcome occurring biochemical failure in 24–72% of cases after radiotherapy and hormone therapy [1–4]. Recently, the 10-years results of two large randomized trials, the

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European Organisation for Research and Treatment of Cancer (EORTC) 22863 and the Trans-Tasman Radiation Oncology Group (TROG) 9601 trials, demonstrated the advantage of combining radiotherapy with androgen suppression in intermediate and high risk patients [5,6]. However, disease-free survival rates were not satisfactory being of 47.7% and 36.0%, respectively for EORTC 22863 and TROG 9601. In particular, the TROG 9601 trial reports a biochemical failure and local progression rates of 52.8% and 13.3%, respectively.

Surgery consisting in radical prostatectomy was employed in a number of randomized trials in patients with high-risk prostate cancer that demonstrated improved outcomes using adjuvant radiotherapy [7]. In particular, extraprostatic disease extension and/or positive surgical margins carried worse prognosis. In this regard, almost 50% of patients with locally advanced disease after radical prostatectomy experience local relapse [1–3]. Based on historical results, surgery can still be considered a treatment option for high risk prostate cancer in selected cases associated, in case of unfavorable features, with radiotherapy that traditionally has been implemented in postoperative setting [8].

Intra-operative radiotherapy (IORT) for prostate cancer was proposed firstly by Abe et al. [9] and by Takahashi et al. [10] at the Kyoto University. More recently, other authors have developed new clinical protocols implementing such technique in intermediate and high-risk disease [11–13].

The rationale for using IORT is related to the technical and biological issues [14]. Prostate exposure during surgical procedure may allow optimal target identification and sparing of surrounding structures. Recent radiobiological studies suggest that using single high doses of radiation may increase the efficacy of the treatment through high tumor cell killing [15].

The purpose of this review is to describe the existing technical approaches of IORT for locally advanced prostate cancer and to discuss the available results of this treatment modality in terms of feasibility, potential advantages, and clinical outcome.

2. Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE, PubMed, Scopus using the search terms “intra-operative”, “radiotherapy”, and “prostate cancer”. Abstracts from international meetings or book chapters were included only when they related directly to previously published work.

3. Technical approaches

IORT was used at the Kyoto University and at the Saitama Cancer Center in Japan as a single treatment or combined with lymph node dissection and/or with pelvic external beam radiotherapy (EBRT) [10,16–20]. The very first approach described by Abe et al. [9] was performed by perineal approach without prostatectomy using 10–14 MeV electron beam with single dose of 28–35 Gy. Fourteen patients were placed in lithotomy position and prostate exposure was obtained through an inverted U-shaped incision in the perineum in order to insert the collimator [10]. This treatment was combined with EBRT to the pelvic nodes to a total dose of 50 Gy with conventional fractionation (Table 1). Other Japanese authors from the Saitama Cancer Center [18–20] preferred to switch from a perineal to a retropubic approach because of the potential risk of rectal damage, impossibility to perform pelvic lymph node dissection, and discomfort of the patient who cannot maintain the seated position for a longtime after the procedure. Kato et al. [20] described also the use of a rectal spacer in order to minimize the dose to the rectum during IORT procedure. In this series of 54 patients, fractionated EBRT was delivered to 30 Gy followed by IORT and pelvic lymph node dissection (Table 1). Of note, prostatectomy was not performed and prostate was left in place after IORT in all Japanese series.

A substantially different treatment approach was adopted by three Italian centers that selected high risk patients based on pre-operative risk factors including PSA level, Gleason score, clinical stage, and number of positive biopsy cores [11–13]. Selection criteria were oriented to intermediate risk patients in the series treated at the Institute “Regina Elena” in Rome [11] and to the high risk patients in the series treated at the European Institute of Oncology in Milan and at the University of East Piedmont in Novara [12,13].

In these three centers, IORT was combined with retropubic radical prostatectomy and pelvic lymphadenectomy after or prior to surgical removal of the prostate gland (Fig. 1). In the Saracino’s series, 34 cases were treated after prostate removal to IORT doses of 16–22 Gy by 7–9 MeV electrons as a single radiation treatment [11]. The dose was prescribed to the 85–90% isodose curve. The IORT procedure was performed after bladder-urethral anastomosis and confirmation of pathological negativity of bilateral obturator nodes. In vivo dosimetry was performed by mosfet dosimeters inserted in rectal and in Foley catheters as a quality assurance procedure [21]. A lucite collimator 4–6 cm in diameter was positioned on the tumor bed covering the bladder-urethral anastomosis and two orthogonal radiographs were taken to check the setup.

Orecchia et al. [12] and Krengli et al. [13] reported on 11 and 38 patients, respectively, treated with IORT during radical prostatectomy before prostate removal. In these series, IORT was used not as a single radiation treatment modality but as an anticipated boost followed by postoperative EBRT. A dose of 10–12 Gy was prescribed to the 90% isodose using 9–12 MeV electrons [12,13]. In these series, surgery was performed by midline subumbilical-pubic incision to approach the prostate. The pelvic fascia was prepared and the IORT procedure started after exposure of the anterior aspect of the prostate, section of the pubo-prostatic ligaments, and control of the deep dorsal vein plexus. The apex of the prostate and the endopelvic urethra were visualized and a stitch was placed