EUROPEAN UROLOGY 73 (2018) 512–518

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorials by Mark Frydenberg and Henry H. Woo on pp. 519–520 and by Douglas Brand and Chris Parker on pp. 521–523 of this issue

Use of Concomitant Androgen Deprivation Therapy in Patients Treated with Early Salvage Radiotherapy for Biochemical Recurrence After Radical Prostatectomy: Long-term Results from a Large, Multi-institutional Series

Giorgio Gandaglia[a,1], Nicola Fossati[a,1], R. Jeffrey Karnes[b], Stephen A. Boorjian[b], Michele Colicchia[b], Alberto Bossi[c], Thomas Seisen[c], Cesare Cozzarini[d], Nadia Di Muzio[d], Barbara Noris Chiorda[d], Emanuele Zaffuto[a], Thomas Wiegel[e], Shahrokh F. Shariat[f], Gregor Goldner[g], Steven Joniau[h], Antonino Battaglia[h], Karin Haustermans[i], Gert De Meerleer[i], Valérie Fonteyne[j], Piet Ost[j], Hendrick Van Poppel[e], Francesco Montorsi[a], Alberto Briganti[a,]*

[a] *Division of Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy;* [b] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [c] *Department of Radiation Oncology, Gustave Roussy Institute, Villejuif, France;* [d] *Department of Radiotherapy, IRCCS Ospedale San Raffaele, Milan, Italy;* [e] *Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany;* [f] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [g] *Department of Radiation Oncology, Medical University of Vienna, Vienna, Austria;* [h] *Department of Urology, University Hospitals Leuven, Leuven, Belgium;* [i] *Department of Radiotherapy, University Hospitals Leuven, Leuven, Belgium;* [j] *Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium*

Article info

Article history:
Accepted November 21, 2017

Associate Editor:
Matthew Cooperberg

Statistical Editor:
Andrew Vickers

Keywords:
Radical prostatectomy
Prostate cancer
Salvage radiotherapy
Androgen deprivation therapy

Abstract

Background: Hormonal manipulation concomitant to salvage radiotherapy (SRT) given for biochemical recurrence (BCR) after radical prostatectomy (RP) improved outcomes in two randomized trials. However, neither of these studies focused on men treated at low prostate-specific antigen (PSA) levels.
Objective: To test if the impact of androgen deprivation therapy (ADT) on metastasis in patients undergoing early SRT varies according to prostate cancer (PCa) features.
Design, setting, and participants: A total of 525 patients received SRT at PSA levels $\leq$2 ng/ml.
Outcome measurements and statistical analyses: Multivariable Cox regression analyses assessed factors associated with metastasis. We tested the hypothesis that the impact of ADT varied according to the risk of metastasis. An interaction with groups (concomitant ADT vs no ADT) and the probability of distant metastasis according to a newly developed model was tested. A nonparametric curve explored the relationship between the risk of metastasis and 10-yr metastasis rates according to ADT.
Results and limitations: Median PSA and radiotherapy dose were 0.42 ng/ml and 66 Gy, respectively. Overall, 178 (34%) patients received ADT. At a median follow-up of 104 mo, 71 patients experienced metastasis. Grade group $\geq$4 (hazard ratio [HR]: 1.66; 95% confidence interval [CI]: 1.01–3.30), pT3b/4 (HR: 2.61; 95% CI: 1.51–4.52), and dose (HR: 0.82; 95% CI: 0.76–0.89) were associated with metastasis. The impact of ADT

[1] These authors contributed equally.
* Corresponding author. Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Milan, Italy. Tel. +39 0226437286; Fax: +39 0226437286.
E-mail address: briganti.alberto@hsr.it (A. Briganti).

https://doi.org/10.1016/j.eururo.2017.11.020

differed according to the risk of metastasis calculated using a multivariable model ($p = 0.01$). This was confirmed when considering patients treated with early SRT ($p = 0.046$), where ADT was associated with a reduction in the rate of metastasis only in eSRT; patients with more aggressive characteristics (ie, pT3b/4 and grade group $\geq$4, or pT3b/4 and PSA at eSRT $\geq$0.4 ng/ml).
Conclusions: The beneficial effect of ADT concomitant to eSRT varied significantly according to disease characteristics, such that only men with more aggressive PCa features benefit from ADT in the eSRT setting for BCR after RP.
Patient summary: The oncological benefits of concomitant androgen deprivation therapy (ADT) in patients undergoing salvage radiotherapy (SRT) vary according to pathological characteristics. Only patients with more aggressive disease characteristics seemed to benefit from the use of hormonal manipulation at the time of early SRT. Conversely, the potential side effects of ADT could be spared in patients with low prostate-specific antigen levels and favorable pathological features.

1. Introduction

A non-negligible proportion of prostate cancer (PCa) patients undergoing radical prostatectomy (RP) will experience biochemical recurrence (BCR) [1,2]. These individuals are at an increased risk of metastasis and, eventually, of dying from PCa [3]. Salvage radiotherapy (SRT) represents the only curative treatment option associated with durable cancer control when delivered in an early setting (namely, eSRT) [4,5]. Two randomized controlled trials (RCTs) demonstrated that concomitant hormonal manipulation at the time of SRT improved oncological outcomes [6,7]. However, the generalizability of these findings might be limited by four main reasons:

1. None of the two studies focused exclusively on eSRT (namely, radiotherapy [RT] administered at prostate-specific antigen [PSA] levels <0.5 ng/ml), which is currently recommended by clinical guidelines [1,5,8–13]. Moreover, a systematic review recently showed that the benefit of hormonal manipulation varies according to pre-SRT PSA [14]. In this context, the RTOG 9601 trial was initially restricted to men with baseline PSA between 0.5 and 4 ng/ml, and those with a PSA between 0.2 and 0.5 ng/ml were considered eligible only after the initiation of the trial.
2. Inclusion of heterogeneous cohorts. For example, more than 10% of patients included the RTOG 9601 trial received SRT for PSA persistence after surgery, which is a risk factor for adverse oncological outcomes after SRT [15].
3. Use of a composite end point evaluated at intermediate follow-up [6]. While in the RTOG 9601 trial the primary end point was overall survival, in the GETUG 16 study the outcome was represented by progression-free survival at a median follow-up of 5 yr.
4. Both studies excluded men treated at higher radiation doses. Despite the lack of available level 1 evidence data supporting the role of dose escalation in the salvage setting, radiobiological models support the use of higher doses [16,17].

To overcome these limitations, we tested the impact of concomitant androgen deprivation therapy (ADT) in a contemporary cohort of men receiving SRT at low PSA levels for BCR after RP. We hypothesized that the beneficial effect of ADT might be limited to patients with more aggressive disease characteristics.

2. Patients and methods

2.1. Study population

After Institutional Review Board approval, 706 patients who received SRT for recurrent PCa after RP between 1996 and 2009 at six tertiary referral institutions were identified. All patients had an undetectable first PSA after surgery (defined as <0.1 ng/ml). All patients received SRT due to BCR after RP, which was defined as a PSA increase within two or more determinations [12]. Patients were excluded if they had missing PSA values at the time of SRT ($n = 38$), missing data on the administration of concomitant ADT ($n = 34$), and undergone previous ADT ($n = 40$). This resulted in a final population of 594 patients. We then focused on node-negative patients ($n = 558$). Owing to their increased risk of metastases [18], patients with PSA levels at SRT >2 ng/ml were excluded. This resulted in a study cohort of 525 patients.

2.2. Covariates

All patients had available data on preoperative PSA, pathological stage, surgical margin status, pathological grade group, RT dose and fields. Prostatectomy specimens were evaluated by high-volume, expert uropathologists. Central pathology review was not performed.

2.3. RT technique

Postoperative RT was delivered to the prostate and seminal vesicle bed at a median (interquartile [IQR]) dose of 66 (65–71) Gy using previously described techniques [8,19,20]. Whole-pelvis RT was administered to 112 patients (21%). The median (IQR) dose delivered to the pelvic nodal area was 50 (50–51) Gy. The decisions to irradiate the pelvic lymph node area and administer concomitant ADT were based on the clinical judgment of each treating physician according to individual patient and cancer characteristics.

2.4. End points

The primary outcome of the study was distant metastasis after SRT. Metastases in the pelvic and retroperitoneal lymph nodes, bones, parenchymal organs, or soft tissues were identified by conventional