Review

Individualization of Adjuvant Therapy After Radical Prostatectomy for Clinically Localized Prostate Cancer: Current Status and Future Directions

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Abstract

Radiation therapy indications in the postprostatectomy setting are evolving. Several retrospective series have identified a number of "high-risk" pathologic features associated with an elevated risk of disease recurrence after radical prostatectomy. More recently, several randomized phase III trials demonstrated superior biochemical relapse-free survival for adjuvant radiation therapy after prostatectomy for patients with these high-risk pathologic features, including positive margin status, extraprostatic extension, and/or seminal vesicle invasion. These series further suggested improvement in distant metastasis control and overall survival after 15 years. However, not all patients with high-risk features experience disease recurrence after surgery alone, and some subsets of patients experience suboptimal disease control and survival despite immediate postoperative radiotherapy. Furthermore, some patients without high-risk features will develop recurrence. The present review discusses the current data and potential future directions to improve individualization of therapy after prostatectomy.

Clinical Genitourinary Cancer, Vol. 14, No. 1, 12-21
Keywords: Adjuvant therapy, Margin involvement, Prostate neoplasms, Radiotherapy, Surgical pathology

Introduction

Radical prostatectomy is often a successful primary management option for men with clinically localized prostate cancer,[1,2] with high rates of long-term disease-free survival.[2,3] Historically, recurrences were identified only by symptomatic recurrence (frequently pelvic or bony sites).[4] However, the development of serum prostate-specific antigen (PSA) testing as a surveillance marker facilitated identification of patients at risk of disease failure at a much earlier stage.[5] Several histopathologic features were found to be associated with an elevated risk of recurrence, including pre- and postoperative PSA levels, prostatectomy specimen Gleason score, surgical margin status, extraprostatic extension (EPE), seminal vesicle involvement (SVI), and lymph node involvement.[3,6] Although patients with high-risk features can enjoy long-term symptom-free survival after surgery, ≤70% of men will experience biochemical (PSA) recurrence within 10 years.[7,8] Several recent phase III randomized trials have demonstrated improved disease control,[9-11] disease-specific survival,[7] and distant metastasis-free survival[7] after immediate postoperative (adjuvant) radiation therapy in the setting of these high-risk features (Table 1). From these data, the benefit of adjuvant radiotherapy appears to be most pronounced for men in good general health (>10-year estimated survival at prostatectomy), with distant metastasis-free and overall survival benefits noted beyond that interval.[7] Despite the use of adjuvant radiation therapy, 35% to 40% of patients randomized to receive radiotherapy will have experienced PSA relapse at 10 years.[7,8] Furthermore, 30% to 40% of patients randomized to observation had not developed PSA relapse at 10 years after prostatectomy. Thus, some patients with

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Submitted: Mar 26, 2015; Accepted: Jul 30, 2015; Epub: Aug 6, 2015

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.07.022

Table 1 Summary of Randomized Trials for Immediate Postoperative (Adjuvant) Radiotherapy for Prostate Cancer

Variable	SWOG 8794	EORTC 22911	German ARO 96-02
Patients enrolled (n)	425	1005	385
Years conducted	1988-1997	1992-2001	1997-2004
Enrollment criteria	PS 0-2, pN0, and pT3a-pT3b or R1	<76 years, PS 0-1, and pN0, pT3a-pT3b or pT2-pT3 R1	pT3-pT4N0
Eligible for randomization	Any postoperative PSA level	<0.4 ng/mL	Undetectable
Stratification	Tumor extent Pre-RP HT	NA	Gleason score <6 vs. >7 Margin positive vs. negative pT3a-T3b vs. pT3c Pre-RP HT
Radiotherapy specifics	<17.5 wk after RP 60-64 Gy PF 3D using ports	<16 wk after RP 50 Gy pelvis plus 10 Gy boost (PF/SVs) 2D isocentric	6-12 wk after RP 60 Gy to PF/SVs 3D with 1-cm PTV
Follow-up protocol	Q3 mo × 2 years, Q6 mo through 5 years, then annually	Q4 mo × 1 years, Q6 mo through 5 years, then annually	Q3 mo × 2 years, Q6 mo through 5 years, then annually
PSA failure definition	PSA >0.4 ng/mL	Increase >0.2 ng/mL above nadir	Two sequential increases
Primary endpoint	DMFS	5-y PFS	5-y PFS
PSA control	10 years	5 years and 10 years	5 years
With RT	65%	74% and 61%	72%
Without RT	36%	53% and 38%	54%
Local failure (%)	NR	10 years	NR
With RT	NA	7%	NA
Without RT	NA	17%	NA
Distant failure	10 years	10 years	NR
With RT	29%	7%	NA
Without RT	39%	7%	NA
Overall survival	10 years	NR	NR
With RT	74%	NA	NA
Without RT	66%	NA	NA

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; ARO = Arbeitsgemeinschaft Radiologische Onkologie; DMFS = distant metastasis-free survival; EORTC = European Organization for Research and Treatment of Cancer; HT = hormone therapy; NA = not applicable; NR = not reported; PF = prostate fossa; PFS = progression-free survival; PS = performance status; PSA = prostate-specific antigen; PTV = planning target volume; Q = every; RP = radical prostatectomy; RT = radiotherapy; SVs = seminal vesicles; SWOG = Southwestern Oncology Group.

high-risk pathologic features will not benefit from immediate adjuvant radiotherapy, and others in this high-risk cohort can be safely followed up with observation. Additionally, some patients without high-risk features will experience recurrence,[12,13] suggesting that as-yet unidentified tumor biologic factors might play a role beyond the traditional histopathology-based risk stratification. The present review discusses the current data and future opportunities for individualizing management after prostatectomy to optimize disease control and minimize unnecessary interventions.

Discussion

Histopathologic Factors

Margin Status. Involvement of the surgical margin or margins by tumor is a well-established risk factor for disease failure in prostate cancer. Although some of these patients have a detectable PSA level after prostatectomy, some do not, and its presence or absence has not seemed to affect the benefit of adjuvant radiotherapy.[8,11,14] Investigators from Korea recently reported their experience with postprostatectomy PSA dynamics and its relationship to disease control.[15] At the study institution, ultrasensitive PSA levels were measured at 2 weeks, 6 weeks, 2 months, and 3 months postoperatively, every 3 months through 1 year, and every 6 months thereafter. Of the 214 patients with involved margins, 97 who had achieved an undetectable PSA level (defined as <0.01 ng/mL) within 6 weeks postoperatively had disease control outcomes comparable to those of margin-negative patients (at a median follow-up of 58 months). However, those whose PSA level reached an undetectable level only after 6 weeks postoperatively had significantly worse PSA control (59.2% vs. 78.8% at 5 years; $P = .004$).

Secondarily, the histologic aggressiveness of the tumor (ie, Gleason score or World Health Organization grade) also predicts for margin involvement and recurrence. Investigators from the Nijmegen Medical Centre reported on a population of 1009 patients who had undergone radical prostatectomy without pre- or post-operative therapy. Of these patients, 249 (25%) had involved surgical margins.[16] Although involvement of a surgical margin was associated with an increased risk of postprostatectomy relapse (41% vs. 12%), neither an increasing number of positive margin foci nor bilaterality of margin involvement was associated with increased risk. Multivariate analysis identified the preoperative PSA level and Gleason score (at prostatectomy) as significantly associated with the 5-year recurrence rates when associated with positive surgical margins.