RESEARCH ARTICLE

Risk Factors for Clinical Metastasis in Men Undergoing Radical Prostatectomy and Immediate Adjuvant Androgen Deprivation Therapy

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Abstract

   Background: Adjuvant androgen deprivation therapy (ADT) is a treatment option for prostate cancer (PC) patients after radical prostatectomy (RP). Although it can achieve a good progression-free survival rate, some patients still develop clinical metastasis. We here investigated risk factors of clinical metastasis in post-prostatectomy patients who received immediate adjuvant ADT. Materials and Methods: We identified 197 patients with non-metastatic PC who underwent RP at our institution between 2000 and 2012, followed by adjuvant ADT. The associations of various clinicopathologic factors with clinical metastasis (primary endpoint) and cancer-specific survival (secondary endpoint) were assessed. Multivariate analysis was conducted using a Cox proportional hazards model. Median follow-up was 87 months after RP. Results: Nine (4.6%) patients developed clinical metastasis and six (3.0%) died from PC. Eight of nine metastatic patients had a pathologic Gleason score (GS) 9 and developed bone metastasis, while the remaining one had pathologic GS 7 and developed metastasis only to para-aortic lymph nodes. On multivariate analyses, pathologic GS ≥9 and regional lymph node metastasis (pN1) were independent predictors of clinical metastasis and pathologic GS ≥9 was an independent predictor of cancer-specific death. Conclusions: Pathologic GS ≥9 and pN1 were independent predictors of clinical metastasis in post-prostatectomy patients who received immediate adjuvant ADT. Furthermore, pathologic GS ≥9 was an indispensable condition for bone metastasis, which may imply that patients with GS ≤8 on adjuvant ADT are unlikely to develop bone metastasis.

Keywords: Adjuvant - androgen deprivation therapy - clinical metastasis - prostate cancer - radical prostatectomy

Introduction

   More than 1,112,000 patients worldwide were estimated to be diagnosed with prostate cancer (PC) in 2012, resulting in more than 307,000 deaths (Ferlay et al., 2013). In Japan, PC is the fourth, most commonly diagnosed cancer in men, with an estimated incidence of 51,534 cases (11.8% among 437,787 cancer patients of all primary sites) in 2008, and accounts for about 9,800 deaths annually in the latest data as of May 2014 (Matsuda et al., 2014). Most men diagnosed in the prostate-specific antigen (PSA) era have favorable disease characteristics that are curable by surgery or radiation therapy. However, the subset of men with high-grade (Gleason score [GS] ≥8) or extraprostatic disease (T3/T4 or lymph node involvement) have a risk of treatment failure as high as 70% when treated with surgery alone (Petrovich et al.,

2002; Roehl et al., 2004; Carver et al., 2006; Nguyen et al., 2009; Dorff et al., 2011). Adjuvant androgen deprivation therapy (ADT), as well as adjuvant radiotherapy, has been a common treatment option for these patients with high risk PC for a long time in Asia (Akaza et al., 2013), but its efficacy has not been well studied.

   Recently, we have reported favorable long-term results of immediate ADT after radical prostatectomy (RP) in Japanese patients with pT3N0 PC, including a 10-year biochemical progression-free survival rate of 88.3% and cancer-specific survival rate of 96.3% after a median follow-up period of 8.2 years (Sato et al., 2014). However, despite such excellent outcomes, some patients still develop clinical metastasis.

   Here we investigated risk factors of clinical metastasis in post-prostatectomy patients who received adjuvant ADT.

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Table 1. Clinicopathologic Features of 197 Prostate Cancer Patients Who Received Adjuvant Androgen Deprivation Therapy Following Radical Prostatectomy

Parameter	Value
Median age, yr (IQR)	67 (62-70)
Median preoperative PSA, ng/mL (IQR)	14.2 (7.95-30.5)
Clinical tumor stage, no. (%)	
T1	58 (29.4)
T2	65 (33.0)
T3/4	74 (37.6)
Pathologic tumor stage, no. (%)	
T2	40 (20.3)
T3a	74 (37.6)
T3b	53 (26.9)
T4	30 (15.2)
Pathologic GS, no. (%)	
5	14 (7.1)
6	20 (10.2)
7	82 (41.6)
8	19 (9.6)
9	61 (31.0)
10	1 (0.5)
Regional lymph node metastasis, no. (%)	27 (13.7)
- Status of positive lymph nodes	
Median no. of positive lymph nodes (IQR)	1 (1-3)
Average no. of positive lymph nodes	2.5
Median no. of removed lymph nodes (IQR)	8 (6-13)
Average no. of removed lymph nodes	10.3
Extraprostatic extension, no. (%)	135 (68.5)
Lymphovascular invasion, no. (%)	119 (60.4)
Positive surgical margin, no. (%)	158 (80.2)
Seminal vesicle invasion, no. (%)	71 (36.0)
Perineural invasion, no. (%)	159 (80.7)
Neoadjuvant hormonal therapy, no. (%)	24 (12.2)
Combined adjuvant radiotherapy, no. (%)	19 (9.6)
Median follow-up, mo (IQR)	87 (44-108)

*IQR, interquartile range; PSA, prostate-specific antigen; GS, Gleason score

Materials and Methods

Reviewing 855 patients who underwent RP at our institution between 2000 and 2012, we identified 197 with non-metastatic (pT2-4N0-1M0) PC who received continuous immediate adjuvant ADT after surgery. This cohort includes 105 patients with pT3N0M0 PC who underwent RP plus immediate adjuvant ADT (Sato et al., 2014). Surgical procedure included bilateral obturator lymph node dissection in all cases. Regional lymph node metastases (pN1) were found in 27 (13.7%) with a median number of positive nodes of one (interquartile range [IQR]: 1-3) out of 8 removed (IQR: 6-13) (Table 1).

We assessed the associations of various clinicopathologic factors with the occurrence of clinical metastasis (the primary endpoint) and cancer-specific survival (the secondary endpoint). Univariate and multivariate analyses were carried out using log-rank tests and Cox proportional hazards model, respectively. Patients who discontinued ADT were counted as censored at the point of discontinuation. The median follow-up was 87 months (IQR: 44-108 months) after RP (Table 1). All statistical analyses were carried out using JMP version 9.0.2 (SAS Institute, Cary, NC, USA). A value of p<0.05 was considered significant.

This study was approved by the Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo.

Results

Nine (4.6%) patients developed clinical metastasis and six (3.0%) died from PC during the follow-up period. Eight of nine metastatic patients had pathologic GS 9 and developed bone metastasis, while the remaining one had pathologic GS 7 and developed metastasis only to para-aortic lymph nodes. In other words, pathologic GS ≥9 was an indispensable condition for bone metastasis in our cohort (Table 2). For reference, the exceptional case with pathologic GS 7 and para-aortic lymph node metastasis was the one which we previously reported to achieve three-year progression-free survival by zoledronic acid administration even after developing aggressive castration-resistant PC (Taguchi et al., 2012). Univariate analysis showed that clinical tumor stage ≥T3, pathologic GS ≥9, pN1, lymphovascular invasion, and seminal vesicle invasion were significantly associated with clinical metastasis and cancer-specific survival (Table 3). Multivariate analysis identified pathologic GS ≥9 and pN1 as independent predictors of clinical metastasis. Pathologic GS ≥9 was also an independent predictor of cancer-specific death (Table 4).

Discussion

ADT is a well-established treatment modality for patients with advanced PC (Ryan et al., 2005) and is also widely used for older patients with local PC (Situmorang et al., 2012). For surgical patients, a survival advantage with adjuvant ADT was also demonstrated in a small (n=98) trial of lymph node-positive patients (Messing

Table 2. Clinicopathologic Features of Nine Prostate Cancer Patients Who Developed Clinical Metastasis

Patient	Pathologic Tumor Stage	Pathologic GS	Regional Lymph Node Metastasis	Metastatic Site	Outcome (follow-up Period, mo)
1	T3a	7	+	Para-aortic lymph nodes	Alive (121)
2	T3b	9	+	Bone	DOD (40)
3	T3a	9	+	Bone	DOD (22)
4	T4	9	+	Bone	DOD (127)
5	T4	9	+	Bone	Alive (103)
6	T3b	9	-	Bone	DOD (12)
7	T3b	9	-	Bone	Alive (34)
8	T4	9	-	Bone	DOD (33)
9	T3b	9	-	Bone	DOD (103)

*PSA, prostate-specific antigen; GS, Gleason score; DOD, died of disease

Table 3. Univariate Analysis Evaluating the Impact of Various Clinicopathologic Factors on the Risks of Clinical Metastasis and Cancer-specific Death in Patients with Prostate Cancer

Variable		No. of patients	Clinical Metastasis, p-value	Cancer-specific Death, p-value
Age, years	<67[†]	97	0.82	0.47
	≥67[†]	100		
Preoperative PSA, ng/mL	≤20[‡]	127	0.83	0.83
	>20[‡]	70		
Clinical tumor stage	≤T2	123	0.02*	0.04*
	≥T3	74		
Pathologic tumor stage	≤T2	38	0.12	0.17
	≥T3	159		
Pathologic GS	≤8	136	0.0001*	0.0001*
	≥9	61		
Regional lymph node metastasis	0	166	<0.0001*	0.004*
	1	31		
Extraprostatic extension	0	62	0.17	0.36
	1	135		
Lymphovascular invasion	0	78	0.01*	0.03*
	1	119		
Positive surgical margin	0	39	0.84	0.78
	1	158		
Seminal vesicle invasion	0	126	0.005*	0.009*
	1	71		
Perineural invasion	0	38	0.12	0.21
	1	159		
Neoadjuvant hormonal therapy	0	173	0.24	0.08
	1	24		
Combined adjuvant radiotherapy	0	178	0.39	0.54
	1	19		

[†]median; [‡]criterion for high risk according to NCCN stratification; *statistically significant; PSA, prostate-specific antigen; GS, Gleason score

Table 4. Multivariate Cox Proportional Hazards Regression Analysis Evaluating the Impact of Various Clinicopathologic Factors on the Risks of Clinical Metastasis and Cancer-specific Death in Patients with Prostate Cancer

Variable	Clinical Metastasis HR (95% CI)	p-value	Cancer-specific Death HR (95% CI)	p-value
Clinical tumor stage		0.15		0.34
≤T2	Reference		Reference	
≥T3	2.98 (0.70-20.4)		2.68 (0.39-52.8)	
Pathologic GS		0.02*		0.008*
≤8	Reference		Reference	
≥9	7.82 (1.40-146.2)		N/C (2.20-)	
Regional lymph node metastasis		0.04*		0.28
0	Reference		Reference	
1	4.20 (1.10-17.1)		2.46 (0.45-13.4)	
Lymphovascular invasion		0.07		0.24
0	Reference		Reference	
1	N/C (0.84-87.5)		N/C (0.31-)	
Seminal vesicle invasion		0.19		0.21
0	Reference		Reference	
1	2.69 (0.64-18.3)		3.40 (0.54-65.7)	

*Statistically significant; GS, Gleason score; N/C, not converged (because no patient existed in the reference cohort)

et al., 1999; Messing et al., 2006). While adjuvant radiotherapy is most commonly used for high risk but lymph node-negative patients after RP in Europe and the United States, adjuvant ADT still has an important position in Asia: The Asia Consensus Statement 2013 in the NCCN Clinical Practice Guidelines in Prostate Cancer states that adjuvant ADT is a candidate treatment option as well as radiotherapy and observation for post-prostatectomy patients with adverse features other than lymph node metastasis (Akaza et al., 2013).

Several studies have shown that RP plus adjuvant ADT provides a good progression-free survival rate. The Southwest Oncology Group (SWOG) S9921 study demonstrated that its ADT-alone control arm of 481 men undergoing adjuvant ADT after RP resulted in a 5-year biochemical progression-free survival rate of 92.5% and a 5-year overall survival rate of 95.9% with a median follow-up of 4.4 years (Dorff et al., 2011). Although being a retrospective study, we also reported a 10-year biochemical progression-free survival rate of 88.3% and

cancer-specific survival rate of 96.3% with a median follow-up of 8.2 years in Japanese patients with pT3N0 PC undergoing adjuvant ADT after RP (Sato et al., 2014). Nevertheless, some patients still develop clinical metastasis and studies evaluating risk factors of clinical metastasis are lacking.

Our study identified pathologic GS ≥9 and pN1 as independent predictors of clinical metastasis in patients with non-metastatic PC who received adjuvant ADT following RP. Furthermore, pathologic GS ≥9 was an indispensable condition for bone metastasis. This may imply that patients with GS ≤8 on adjuvant ADT are unlikely to develop bone metastasis. The results of other studies support these findings. Sundi et al. (2014) reviewed 753 men with National Comprehensive Cancer Network (NCCN), high-risk, localized PC (GS sum 8-10, PSA>20 ng/ml, or clinical stage ≥T3a). They defined very-high-risk localized PC as primary Gleason pattern 5 present on biopsy, five or more cores with GS 8-10, or multiple NCCN high-risk features, and indicated that patients meeting these criteria were at significantly increased risks of metastasis and cancer-specific mortality. Although the treatment modality and time of administration differed, Jackson et al. (2013) demonstrated that Gleason pattern 5 was the strongest pathologic predictor of biochemical recurrence, metastasis, and cancer-specific death in patients receiving salvage radiation therapy following RP. The both studies noted the impact of Gleason pattern 5 on clinical metastasis and cancer-specific death, which may be consistent with our results given that patients with GS ≥9 necessarily demonstrate Gleason pattern 5.

With respect to pN1, a randomized prospective trial demonstrated a survival benefit of adjuvant ADT after RP in the setting of positive lymph nodes, as stated above (Messing et al., 1999; Messing et al., 2006). According to a recent retrospective investigation by Abdollah et al. (2014), which reviewed 1,107 patients with pN1 PC, pathologic GS ≥8, positive surgical margin, number of positive lymph nodes, and combined adjuvant radiotherapy were significant predictors of cancer-specific mortality. In contrast, the current study found no effect of combined adjuvant radiotherapy on cancer-specific survival (Table 3), possibly because the follow-up period was too short.

As in other similar studies, preoperative PSA >20ng/ml (the criterion for high risk according to both the NCCN (Mohler et al., 2010) and D'Amico's risk stratifications (D'Amico et al., 1998) was not associated with clinical metastasis or cancer-specific mortality. The value of 20ng/ml was established to stratify patients at risk of biochemical recurrence (D'Amico et al., 1998), and a higher threshold value may need to be considered for clinical metastasis and cancer-specific mortality. Indeed, we confirmed that preoperative PSA became a significant predictor of clinical metastasis using a cutoff value of >50ng/ml, and of cancer-specific death at a cutoff value of 100ng/ml (data not shown).

Our study was limited by being a retrospective analysis of a limited number of cases at a single institution. Further studies with larger populations are needed to confirm these results. In addition, ADT is associated with some real risks related to metabolic syndrome, which should be taken into account along with the antitumor efficacy (McGrowder et al., 2012).

In conclusion, adjuvant ADT provides compelling survival benefits in high-risk PC patients after RP, but patients with high GS (≥9) still carry a risk of bone metastasis and cancer-specific death. These patients therefore require special attention and might deserve consideration of additional treatment such as combined radiotherapy.

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