RESEARCH ARTICLE

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

Satoru Taguchi, Hiroshi Fukuhara*, Shigenori Kakutani, Yuta Takeshima, Hideyo Miyazaki, Motofumi Suzuki, Tetsuya Fujimura, Tohru Nakagawa, Yasuhiko Igawa, Haruki Kume, Yukio Homma

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

Asian Pac J Cancer Prev, **15 (24)**, 10729-10733

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.

*Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan *For correspondence: hfukuhara-jua@umin.ac.jp*

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	≤20ǂ	127	0.83	0.83
	>20ǂ	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; ǂcriterion 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.

References

Abdollah F, Karnes RJ, Suardi N, et al (2014). Predicting survival of patients with node-positive prostate cancer following multimodal treatment. *Eur Urol*, **65**, 554-62.

Akaza H, Cheng JC, Chung BH, et al (2013). NCCN clinical practice guidelines in oncology (NCCN Guidelines®)-asia consensus statement: prostate cancer version 2.2013. http://www.nccn.org/international/PDF/prostate-asia.pdf.

Carver BS, Bianco FJ Jr, Scardino PT, Eastham JA (2006). Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol*, **176**, 564-8.

D'Amico AV, Whittington R, Malkowicz SB, et al (1998). Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*, **280**, 969-74.

Dorff TB, Flaig TW, Tangen CM, et al (2011). Adjuvant androgen deprivation for high-risk prostate cancer after radical prostatectomy: SWOG S9921 study. *J Clin Oncol*, **29**, 2040-5.

Ferlay J, Soerjomataram I, Ervik M, et al (2013). GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: Intl Agency Res Cancer. Available from: http://globocan.iarc.fr, accessed on day/month/year.

Jackson W, Hamstra DA, Johnson S, et al (2013). Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following radical prostatectomy. *Cancer*, **119**, 3287-94.

Matsuda A, Matsuda T, Shibata A, et al (2014). The Japan cancer surveillance research group. cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the monitoring of cancer incidence in Japan (MCIJ) Project. *Jpn J Clin Oncol*, [E-pub ahead of print].

McGrowder DA, Jackson LA, Crawford TV (2012). Prostate cancer and metabolic syndrome: is there a link? *Asian Pac J Cancer Prev*, **13**, 1-13.

Messing EM, Manola J, Sarosdy M, et al (1999). Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med*, **341**, 1781-8.

Messing EM, Manola J, Yao J, et al (2006). Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*, **7**, 472-9.

Mohler J, Bahnson RR, Boston B, et al (2010). NCCN clinical practice guidelines in oncology: prostate cancer. *J Natl Compr Canc Netw*, **8**, 162-200.

Nguyen CT, Reuther AM, Stephenson AJ, Klein EA, Jones JS (2009). The specific definition of high risk prostate cancer has minimal impact on biochemical relapse-free survival. *J Urol*, **181**, 75-80.

Petrovich Z, Lieskovsky G, Stein JP, Huberman M, Skinner DG (2002). Comparison of surgery alone with surgery and adjuvant radiotherapy for pT3N0 prostate cancer. *BJU Int*,

89, 604-11.
Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ (2004). Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: Long-term results. *J Urol*, **172**, 910-4.
Ryan CJ, Small EJ (2005). Early versus delayed androgen deprivation for prostate cancer: new fuel for an old debate. *J Clin Oncol*, **23**, 8225-31.
Sato YT, Fukuhara H, Suzuki M, et al (2014). Long-term results of radical prostatectomy with immediate adjuvant androgen deprivation therapy for pT3N0 prostate cancer. *BMC Urol*, **14**, 13.
Situmorang GR, Umbas R, Mochtar CA, et al (2012). Prostate cancer in younger and older patients: do we treat them differently? *Asian Pac J Cancer Prev*, **13**, 4577-80.
Sundi D, Wang VM, Pierorazio PM, et al (2014). Very-high-risk localized prostate cancer: definition and outcomes. *Prostate Cancer Prostatic Dis*, **17**, 57-63.
Taguchi S, Fujimura T, Kume H, Homma Y (2012). Zoledronic acid administration in aggressive castration-resistant prostate cancer. *Asian Pac J Cancer Prev*, **13**, 6539-40.