Conflict of interest

None declared.

References

1 Van Kerrebroeck P, Abrams P, Chaikin D *et al.* The standardization of terminology in nocturia: report from the standardization subcommittee of the International Continence Society. *Neurourol. Urodyn.* 2002; **21**: 179–83.

2 Homma Y, Yamaguchi O, Hayashi K *et al.* Epidemiologic survey of lower urinary tract symptoms in Japan. *Urology* 2006; **68**: 560–4.

3 Abrams P, Cardozo L, Fall M *et al.* The standardization of terminology in nocturia: report from the standardization sub-committee of the International Continence Society. *Neurourol. Urodyn.* 2002; **21**: 179–83.

4 Tikkinen KA, Tammela TL, Huhtala H *et al.* Is nocturia equally common among men and women? A population based study in Finland. *J. Urol.* 2006; **175**: 596–600.

5 Tikkinen KA, Johnson TM 2nd, Tammela TL *et al.* Nocturia frequency, bother and quality of life: how often is too often? A population-based study in Finland. *Eur. Urol.* 2010; **57**: 488–96.

6 Asplund R, Marnetoft SU, Selander J *et al.* Nocturia in relation to somatic health, mental health and pain in adult men and women. *BJU Int.* 2005; **95**:816–9.

7 Asplund R. Mortality in the elderly in relation to nocturnal micturition. *BJU Int.* 1999; **84**:297–301.

8 Tikkinen KAO, Auvinen A, Johnson II TM *et al.* A systematic evaluation of factors associated with nocturia—The Population based FINNO Study. *Am. J. Epidemiol.* 2009; **170**: 361–8.

9 Irwin DE, Milsom I, Kopp Z *et al.* Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC Study: Impact of overactive bladder. *Eur. Urol.* 2009; **56**: 14–20.

10 Homma Y, Yoshida M, Yamanishi T, Gotoh M. Core lower urinary tract symptom (CLSS) questionnaire: a reliable tool in the overall assessment of lower urinary tract symptoms. *Int. J. Urol.* 2008; **15**: 816–20.

11 Soldatos CR, Dikeos DG, Paparrigopoulos TJ. Athens Insomnia Scale: validation of an instrument based on ICD-10 criteria. *J. Psychosom. Res.* 2000; **48**: 555–60.

12 Soldatos CR, Allaert FA, Ohta T, Dikeos DG. How do individuals sleep around the world? Results from a single-day survey in ten countries. *Sleep Med.* 2005; **6**: 5–13.

13 Barry MJ, Fowler FJ Jr, O'Leary MP *et al.* The American Urological Association symptom index for benign prostatic hyperplasia. The measurement Committee of the American Urological Association. *J. Urol.* 1992; **148**: 1549–57.

14 Homma Y, Yamaguchi O, Kageyama S *et al.* Nocturia in the adult: classification on the basis of largest voided volume and nocturnal urine production. *J. Urol.* 2000; **163**: 777–81.

15 Farrahi J, Nakhaee N, Sheibani V *et al.* Psychometric properties of the Persian version of the Pittsburgh Sleep Quality Index addendum for PTSD (PSQI-A). *Sleep Breath.* 2009; **13**: 259–62.

16 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chron. Dis.* 1987; **40**: 373–83.

17 Alvarez-Nebreda ML, Jimenez AB, Rodrigues P *et al.* Epidemiology of hip fracture in the elderly in Spain. *Bone* 2008; **42**: 278–85.

18 Nakagawa H, Niu K, Hozawa A *et al.* Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. *J. Urol.* 2010; **184**:1413–8.

19 Yokoyama O, Aoki Y, Tsujimura A, *et al.* α(1)-adrenoreceptor blocker naftopidil improves sleep disturbance with reduction in nocturnal urine volume. *World J. Urol.* 2011; **29**: 233–8.

20 Udo Y, Nakao M, Honjo H *et al.* Analysis of nocturia with 24-h urine volume, nocturnal urine volume, nocturnal bladder capacity, and length of sleep duration: concept for effective treatment modality. *BJU Int.* 2010; **107**: 791–8.

21 Buysse DJ, Reynolds CF III, Monk TH *et al.* The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989; **28**: 193–213.

22 Shinohara Y, Yamaguchi T. Outline of the Japanese guidelines for the management of stroke 2004 and subsequent revision. *Int. J. Stroke* 2008; **3**: 55–62.

23 Shyh-Chyi C, Alex TL, Kuang-Kuo C *et al.* Multifocal nature of male nocturia. *Urology* 2006; **67**: 541–4.

24 Hashim H, Abrams P. How should patients with an overactive bladder manipulate their fluid intake? *BJU Int.* 2008; **102**: 62–6.

25 Soda T, Masui K, Okuno H *et al.* Efficacy of nondrug lifestyle measures for the treatment of nocturia. *J. Urol.* 2010; **184**: 1000–4.

26 De Groat WC. Integrative control of the lower urinary tract: preclinical perspective. *Brit. J. Pharmacol.* 2006; **147**: 25–40.

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

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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.

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.

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Case Report

Intrascrotal Dedifferentiated Leiomyosarcoma Originating from Dartos Muscle

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A 46-year-old man, who had visited our hospital complaining of a small intrascrotal nodule ten years ago, returned to us because of the rapid growth of the nodule. Computed tomography revealed a heterogeneously enhanced intrascrotal tumor of approximately 4×3 cm. The tumor and the right testis were excised with the adhered right scrotal skin. The pathological diagnosis was pleomorphic leiomyosarcoma with dedifferentiation originating from the dartos muscle. Urological dedifferentiated leiomyosarcomas are rarely reported and the clinical features are mostly unknown. This is the first report to describe the dedifferentiated leiomyosarcoma of the dartos muscle.

1. Introduction

Dedifferentiation is a well-recognized process in several bone and soft tissue tumors, including liposarcoma, chondrosarcoma, periosteal osteosarcoma, chordoma, and solitary fibrous tumor [1]. However, dedifferentiation of leiomyosarcomas is very rare. Herein we report a case of dedifferentiated leiomyosarcoma originating from dartos muscle.

2. Case Presentation

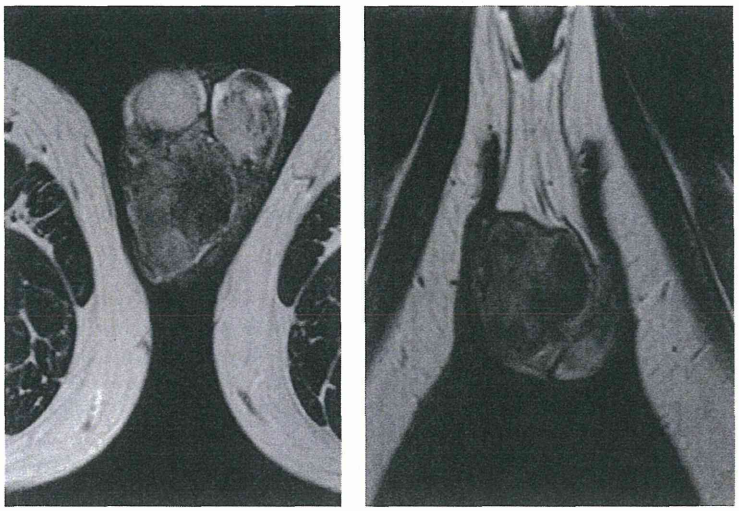
In 2004, a 46-year-old man visited our hospital with a complaint of a small intrascrotal nodule and was placed under observation. In January 2014, he noticed rapid growth of the nodule and visited us again. Physical examination showed a mass in the scrotum near the right testis. Blood tests yielded no specific results. Contrast-enhanced computed tomography revealed a heterogeneously enhanced tumor of approximately 4 × 3 cm. Magnetic resonance imagingshowed a heterogeneous signal in T2 weighted image and early contrast enhancement and washout (Figure 1). There was no evidence of metastasis. Under clinical diagnosis of a malignant intrascrotal tumor, we excised the scrotal tumor with the adhered skin and the right testis. The tumor was yellow in color and 4.7 cm in the maximum diameter. It was located beneath the scrotal skin, apart from the spermatic cord or testis (Figure 2).

Microscopically, the tumor consisted of two different components: leiomyosarcoma and malignant fibrous histiocytoma-like dedifferentiated sarcoma (Figure 3). Immunohistochemistry detected dedifferentiated components of leiomyosarcoma, which were characterized by lack of staining with muscle markers except for caldesmon (Figure 4, Table 1). The pathological diagnosis was pleomorphic leiomyosarcoma with dedifferentiation originating from the dartos muscle of the right scrotum. Immunohistochemical stains for MDM2 and CDK4 were negative; therefore, we excluded dedifferentiated liposarcoma with myogenic differentiation. Although the surgical margin of specimen was negative, there were multiple tumor invasions to peripheral veins. The dermis was invaded, but the epidermis was intact.

The patient had no evidence of recurrence at six months after the operation.

3. Discussion

Soft tissue sarcomas are a heterogeneous group of nonosseous tumors that arise from the embryonic mesoderm [2]. In this group of tumors, genitourinary (GU) sarcoma is relatively



(a) (b)

FIGURE 1: MRI T2 transverse (a) and coronal (b) images show a mass in the right paratesticular region.

FIGURE 2: Macroscopic finding. The mass is separated from the testis and epididymis.

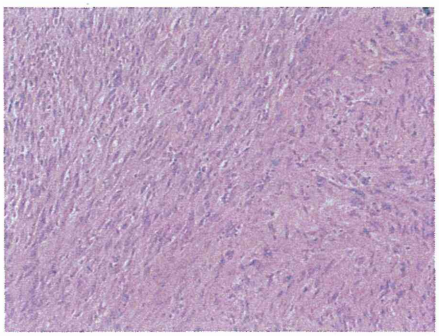


FIGURE 3: Microscopic finding. Spindle shaped leiomyosarcoma cells (right side) and what appeared to be MFH with a high mitotic rate (left side). Hematoxylin and eosin stain ×20 (upper).

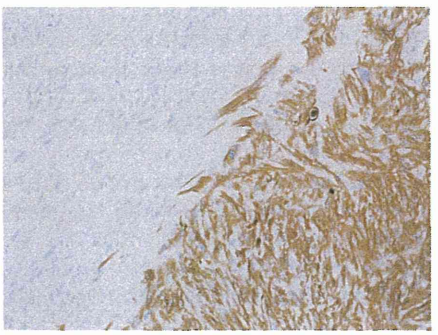


FIGURE 4: Leiomyosarcoma (right) is stained by antibody against calponin but dedifferentiated leiomyosarcoma (left) is not. ×20 (lower).

rare. It is estimated that approximately 10,000 new patients are yearly diagnosed with soft tissue sarcomas in the USA [3], of which GU tract sarcomas consist of 2.1% only [4]. Dotan et al. reported that among 131 GU tract sarcomas the most common histological type was leiomyosarcoma (19%) [2]. Coleman et al. reported that the spermatic cord was the most common site of GU sarcomas (30%) [5]. Of 24 cases of leiomyosarcoma of paratesticular region, only one case was reported to have the origin in the dartos muscle [6]. Our case is the first report of dedifferentiated leiomyosarcoma originating from the dartos muscle.

Chen et al. reported that dedifferentiated leiomyosarcoma was seen in 1.4% of all leiomyosarcomas consulted from 1991 to 2007 [1]. In their report, these dedifferentiated leiomyosarcomas lacked the characteristic immunohistochemical staining of differentiated leiomyosarcoma for muscle-specific actin, smooth muscle actin, desmin, and CD34 [1]. Our case showed the similar features; that is, the differentiated component showed to be strongly positive for muscle markers, but the dedifferentiated component was negative (Table 1).

As for grading systems of sarcomas, the French Federation of Cancer Centers Sarcoma Group grading system

Table 1: Immunostaining of our case.

	Smooth muscle sarcomatoid	Malignant fibrous histiocytoma-like tumor
Vimentin	++	++
α-Smooth muscle actin	++	−
Desmin	++	−
Muscle-specific actin	++	−
Calponin	++	−
Caldesmon	++	+
CD99	Focal+	+
CDK4	−	−
MDM2	−	−
S100	−	−
CD34	−	−
AE1/AE3	−	−
CAM5.2	−	−
MIB-1 index	5%	50%

has been shown to be reproducible among pathologists and correlate with the clinical outcome [7, 8]. In this French system, mitotic activity and the amount of tumor necrosis are scored individually, and these scores are summed up to give a final score of the sarcoma grade [7]. Following this grading system, the score of differentiation of our case was three, the score of necrosis one, and the score of mitotic activity three. The total score was seven, and our case was rated as grade 3.

The optimum local and systemic treatment for these tumors remains controversial, but there is a general consensus that all paratesticular sarcomas in adults should be managed with complete resection, including high ligation of the spermatic cord [7]. Prognosis of GU sarcomas depends on tumor size, grade, stage, histologic type, and lymph node involvement [9–13]. Froehner et al. indicated the tumor size over 5 cm as an important prognostic factor [14]. Of 14 patients of paratesticular leiomyosarcoma, four (29%) had local recurrences and one had metastases [6]. Galosi et al. recommended adjuvant radiation after radical surgery for the high rate of local recurrences [15]. Chen et al. reported a worse prognosis of dedifferentiated sarcomas compared with differentiated sarcomas; of 13 dedifferentiated leiomyosarcomas, metastasis occurred in five (38%) and local recurrence in five (38%) [1]. Close follow-up is needed because of a high frequency of recurrence and metastasis of dedifferentiated leiomyosarcoma.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] E. Chen, F. O'Connell, and C. D. M. Fletcher, "Dedifferentiated leiomyosarcoma: clinicopathological analysis of 18 cases," *Histopathology*, vol. 59, no. 6, pp. 1135–1143, 2011.

[2] Z. A. Dotan, R. Tal, D. Golijanin et al., "Adult genitourinary sarcoma: the 25-year memorial sloan-kettering experience," *Journal of Urology*, vol. 176, no. 5, pp. 2033–2039, 2006.

[3] A. Jemal, T. Murray, E. Ward et al., "Cancer statistics, 2005," *CA: A Cancer Journal for Clinicians*, vol. 55, no. 1, pp. 10–30, 2005.

[4] A. Stojadinovic, D. H. Y. Leung, P. Allen, J. J. Lewis, D. P. Jaques, and M. F. Brennan, "Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables," *Journal of Clinical Oncology*, vol. 20, no. 21, pp. 4344–4352, 2002.

[5] J. Coleman, M. F. Brennan, K. Alektiar, and P. Russo, "Adult spermatic cord sarcomas: management and results," *Annals of Surgical Oncology*, vol. 10, no. 6, pp. 669–675, 2003.

[6] C. Fisher, J. R. Goldblum, J. I. Epstein, and E. Montgomery, "Leiomyosarcoma of the paratesticular region," *The American Journal of Surgical Pathology*, vol. 25, no. 9, pp. 1143–1149, 2001.

[7] B. Khoubehi, V. Mishra, M. Ali, H. Motiwala, and O. Karim, "Adult paratesticular tumours," *BJU International*, vol. 90, no. 7, pp. 707–715, 2002.

[8] J. M. Coindre, P. Terrier, N. B. Bui et al., "Prognostic factors in adult patients with locally controlled soft tissue sarcoma: a study of 546 patients from the French Federation of Cancer Centers Sarcoma Group," *Journal of Clinical Oncology*, vol. 14, no. 3, pp. 869–877, 1996.

[9] N. Mondaini, D. Palli, C. Saieva et al., "Clinical characteristics and overall survival in genitourinary sarcomas treated with curative intent: a multicenter study," *European Urology*, vol. 47, pp. 468–473, 2005.

[10] D. Rodríguez, G. W. Barrisford, A. Sanchez, M. A. Preston, E. I. Kreydin, and A. F. Olumi, "Primary spermatic cord tumors: disease characteristics, prognostic factors, and treatment outcomes," *Urologic Oncology: Seminars and Original Investigations*, vol. 32, no. 1, pp. 52.e19–52.e25, 2014.

[11] R. Stefano, D. Anant, H. James et al., "Prognostic factors and outcome of spermatic cord sarcoma," *Annals of Surgical Oncology*, vol. 21, no. 11, pp. 3557–3563, 2014.

[12] M. T. Ballo, G. K. Zagars, P. W. Pisters, B. W. Feig, S. R. Patel, and A. C. Von Eschenbach, "Spermatic cord sarcoma: outcome, patterns of failure and management," *Journal of Urology*, vol. 166, no. 4, pp. 1306–1310, 2001.

[13] V. T. H. Yuen, S. D. Kirby, and Y. C. Woo, "Leiomyosarcoma of the epididymis: 2 cases and review of the literature," *Journal of the Canadian Urological Association*, vol. 5, no. 6, pp. E121–E124, 2011.

[14] M. Froehner, A. Lossnitzer, A. Manseck, R. Koch, B. Noack, and M. P. Wirth, "Favorable long-term outcome in adult genitourinary low-grade sarcoma," *Urology*, vol. 56, no. 3, pp. 373–377, 2000.

[15] A. B. Galosi, M. Scarpelli, R. Mazzucchelli et al., "Adult primary paratesticular mesenchymal tumors with emphasis on a case presentation and discussion of spermatic cord leiomyosarcoma," *Diagnostic Pathology*, vol. 9, no. 1, article 90, 2014.

Original Study

Adjuvant Chemotherapy Is Possibly Beneficial for Locally Advanced or Node-Positive Bladder Cancer

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Abstract

The role of adjuvant chemotherapy (AC) after radical cystectomy (RC) for bladder cancer remains controversial. In this retrospective study, we showed that cisplatin-based AC improves survival in locally advanced or node-positive bladder cancer, especially in node-positive cases. On multivariate analyses, AC was an independent predictive factor for both recurrence-free survival (RFS) and cancer-specific survival (CSS), along with surgical margin status and lymphovascular invasion.

Background: This study aimed to evaluate the outcomes of cisplatin-based adjuvant chemotherapy (AC) after radical cystectomy (RC) in non–organ-confined bladder cancer. **Methods:** Sixty-one patients who did not receive neoadjuvant chemotherapy (NAC) underwent RC for locally advanced (pT3-4) or node-positive (pN1-3) bladder cancer, or both, between 1990 and 2012. Of these patients, 39 (64%) received cisplatin-based AC after RC (AC group) and the remaining 22 patients (36%) did not (non-AC group). Cancer-specific survival (CSS) and recurrence-free survival (RFS) were compared between the groups. **Results:** The AC group was significantly younger ($P = .004$), but no significant differences were noted between the groups for pT stage, pN stage, nuclear grade, renal function, and salvage chemotherapy rates after recurrence. During a follow-up of 29 months (median), 40 patients (67%) experienced recurrence/metastasis and 34 (56%) died of recurrent bladder cancer. The AC group showed better RFS than the non-AC group, but the difference was not statistically significant (median survival time [MST], 23.7 vs. 11.4 months, respectively; $P = .154$). CSS was significantly better for the AC group than for the non-AC group (MST, 57.4 vs. 17.9 months, respectively; $P = .008$). On multivariate analysis, AC was an independent predictive factor for both RFS (hazard ratio [HR], 0.325; $P = .005$) and CSS (HR, 0.186; $P < .001$), along with surgical margin status and lymphovascular invasion (LVI). In a subgroup analysis of 31 node-positive cases, the AC group had a significantly better CSS compared with the non-AC group ($P = .029$). Analysis of node-negative cases (n = 30) yielded no significant benefit for AC. **Conclusion:** Our observations suggest that postoperative cisplatin-based AC improves survival in locally advanced or node-positive bladder cancer, especially in node-positive cases.

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Keywords: Adjuvant chemotherapy, Clinical outcome, Muscle-invasive bladder cancer, Urinary bladder cancer, Urothelial carcinoma

Introduction

Urinary bladder cancer is the second most common cancer of the genitourinary system.[1] An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide.[1] Radical cystectomy (RC) with pelvic lymph node dissection is a standard treatment for muscle-invasive and high-risk non–muscle-invasive bladder cancer.[2] Despite the advances in surgical technique

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