Cryobiology 68 (2014) 79–83

Contents lists available at ScienceDirect

Cryobiology

journal homepage: www.elsevier.com/locate/ycryo

Percutaneous cryotherapy for metastatic bladder cancer: Experience with 23 patients ☆

Zhou Liang [a,b,1], Yao Fei [a,1], Niu Lizhi [a,b,c,1], Zeng Jianying [b,c], Zhang Zhikai [a], Chen Jibing [a,b,*], Li Jialiang [a,c,*], Xu Kecheng [a,c]

[a] Fuda Cancer Hospital, Jinan University School of Medicine, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China
[b] Fuda Institute of Lung Cancer, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China
[c] Fuda Institute of Cryosurgery for Cancer, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China

ARTICLE INFO

Article history:
Received 8 August 2013
Accepted 16 December 2013
Available online 22 December 2013

Keywords:
Metastatic bladder cancer
Percutaneous cryoablation
Progression-free survival

ABSTRACT

Bladder cancer is the most common malignancy of the urinary tract and in many patients is metastatic at diagnosis. Chemotherapy is the standard treatment for these patients but has serious side effects and in many patients is not tolerated. To avoid the side effects of systemic chemotherapy, patients with late stage bladder cancer have sought cryotherapy in our hospital. We reviewed data for the past 4 years to evaluate the safety and efficiency of percutaneous cryotherapy in 23 patients. Within 3 days after cryosurgery, all complications of bladder cancer (e.g. hematuria, urinary irritation, hypogastralgia, lumbago) had decreased to some degree. No new complications (e.g. bladder perforation) occurred and all complications had disappeared completely after 2 weeks. The progression-free survival (PFS) of these patients was 14 ± 8 months. There was no effect on PFS of tumor location or histopathology; however, differentiation status and tumor size influenced the therapeutic effect of percutaneous cryoablation. In conclusion, percutaneous cryotherapy may be a safe and efficacious therapeutic option in the treatment of metastatic bladder cancer.

Introduction

As of 2013, bladder cancer is estimated to be the fourth most common cancer in new cancer cases and the eighth most common cause of death among all types of cancer in the USA [18]. At the time of diagnosis, approximately 15% of bladder cancers have penetrated the bladder wall and spread, mostly into regional organs (prostate gland, uterus, vagina, or pelvic and abdominal cavity); less often, distant metastasis has occurred. The standard treatment for noninvasive bladder cancer is transurethral resection and intravesical therapy; in patients with metastatic disease, these therapies are obviously useless and systemic chemotherapy is the only treatment that has been shown to improve survival [9,16].

Cryosurgery, which can induce tissue necrosis by ice ball formation, has been used as an alternative therapeutic approach in bladder cancer for half a century. The effects of cryoablation on the bladder were investigated in dogs by McDonald et al. in 1950; typical necrotic lesions were produced [10]. Recently, using modern technology, Permpongkosol et al. investigated the morphologic changes caused by percutaneous full-thickness bladder cryoablation in pigs and achieved controllable transmural necrosis with single and repeated cycles, with no bladder perforation [17]. With the advent of argon–helium cryosurgery and improvements in medical imaging, percutaneous cryosurgery has been used as a novel therapeutic approach to the treatment of benign and malignant tumors, especially unresectable tumors [9]. So, the use of percutaneous cryotherapy in the treatment of metastatic bladder cancer is experimental, and many factors might assist the treatment to success, including the good visibility of the ice ball on computed tomography (CT), close concordance between the area covered by the ice ball and the area of complete necrosis [6,14] and avoidance of damage to the collagenous architecture of the bladder, prostate gland and uterus [7].

In this retrospective study, 4 years of follow-up data for 23 patients obtained from our hospital's database were analyzed to investigate the safety and efficacy of percutaneous cryotherapy in the treatment of metastatic bladder cancer.

☆ *Statement of funding:* This work was supported by Tumor Researching Fund from the Fuda Cancer Hospital, Guangzhou, China.

* Corresponding authors at: Fuda Cancer Hospital, Jinan University School of Medicine, No. 2 Tangdexi Road, Tianhe District, Guangzhou 510665, China. Fax: +86 (020) 38993994 8700.

E-mail addresses: fudaclab@gmail.com (C. Jibing), fudaclab@gmail.com (L. Jialiang).

[1] These authors contributed equally to this work and shared the first author.

0011-2240/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cryobiol.2013.12.004

Materials and methods

Ethics

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Patient selection

Between October 2007 and September 2011, 23 patients with metastatic bladder cancer met our inclusion criteria and were enrolled in the study. These patients had refused to undergo systemic chemotherapy and sought treatment directly in our hospital or after failure of previous chemotherapy. Ideal patients for bladder cryoablation are those with: Karnofsky performance status score $\geqslant 70$; platelet count $\geqslant 80 \times 10^9$/L; white blood cell count $\geqslant 3 \times 10^9$/L; neutrophil count $\geqslant 2 \times 10^9$/L; and no cystitis or urinary tract infection. The diagnosis was confirmed by radiologic imaging and fine needle aspiration biopsy. The common presenting symptoms were gross or microscopic hematuria, urinary irritation (in the form of frequency, urgency or dysuria), hypogastralgia and lumbago. All patients had a single tumor in the bladder and were in the metastatic stage of the disease.

Cryoablation procedure

With the patient supine, the tumor was located by CT and the middle abdomen or groin was used for puncture points according to the tumor's position. Percutaneous cryotherapy was performed on all patients, with the complete cryoablation of all obvious intra- and extracystic masses. Cryosurgery was performed using an argon gas based cryosurgical unit (Endocare, Irvine, CA, USA) and cryoprobes of 1.7 mm diameter (Endocare); one to four cryoprobes were inserted into the mass from the abdominal skin and two freeze/thaw cycles were performed, each reaching a temperature of −120 °C at the tip of the probe. The duration of freezing was dependent on the achievement of an ice ball, visible as a low density area under CT guidance (Fig. 1). Generally, the tumor was frozen for a maximal time of 15 min and thawed for 5 min; this procedure was then repeated. A margin of at least 0.5 cm of normal tissue was frozen circumferentially around the tumor. During the freezing process, attention was paid to avoiding injury to the ureter, urethra, prostate, vagina, uterus and bowel. For masses of 1–1.9 cm in longest diameter, one cryoprobe was used to ensure freezing of the entire tumor; two cryoprobes were necessary for masses of 2–3.9 cm and three or four cryoprobes for tumors of 4–5.9 cm or 6–8 cm, respectively. Compression bandaging was applied to the puncture points after procedure. If the patient can urinate normally and no obvious postoperative hematuria, showing that no cancer plug or severe bleeding, bladder irrigation was usually begun the night after cryosurgery (physiologic saline, daily use 100 ml), otherwise bladder irrigation will be performed at once and continued for 3–5 days until hematuria had disappeared completely.

Tumors in organs other than the bladder (e.g. liver and abdomen) were usually percutaneously ablated during the same procedure as the bladder tumor (so-called "comprehensive cryosurgery" [2,3,11,15]), small satellite lesions will be irrelevant to the outcome.

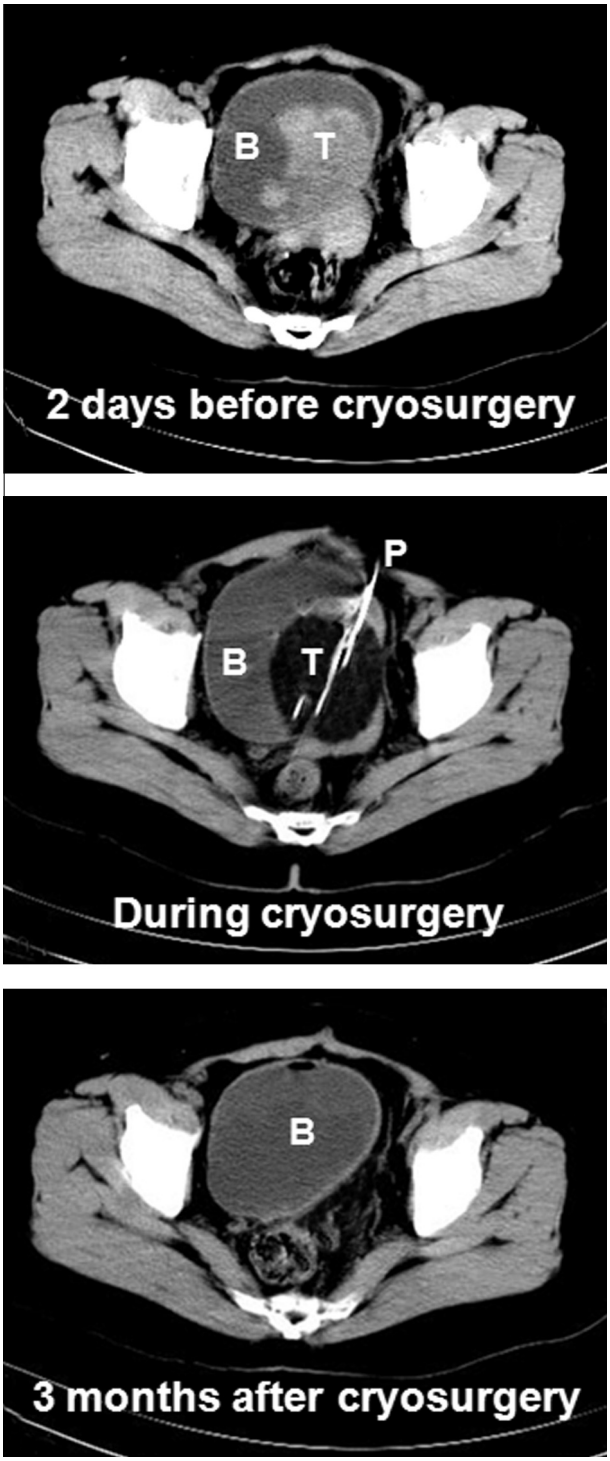

Fig. 1. CT images of a patient with cancer in the right wall of the bladder. Two days before cryosurgery, the tumor (T) occupied more than half of the bladder (B). During cryosurgery with three probes (P), the ice ball grew gradually, surrounded the tumor and formed a low density area. Three months after cryosurgery, the structure of the bladder wall remained intact and tumor inside and outside the bladder had disappeared.

Evaluation and statistical analysis

Complications were recorded and classified in accordance with the Common Terminology Criteria of Adverse Events v4.0. Radiographic local tumor control was assessed using image-guided tumor ablation criteria [5]. A Wilcoxon matched pairs signed rank

Table 1
Data for 23 patients who underwent percutaneous cryotherapy.

No.	First admission date (m/d/y)	Gender/ age	Pathologic type	Differentiation status	Tumor longest diameter	Progression-free survival	Primary location in bladder	Metastatic sites	Complications before cryosurgery	Complications after cryosurgery
1	10/4/2007	M/62	TCC	Well	2.2	16	Left wall	Abdomen	Hematuria	Hematuria
2	8/31/2008	M/64	TCC	Well	3.7	19	Back wall	Abdomen	Hematuria	Hematuria
3	9/16/2008	M/57	SCC	Poor	7.3	12	Anterior wall	Abdomen	Hematuria, Urinary irritation, Abdominal pain	Hematuria
4	9/25/2008	M/58	SCC	Poor	4.5	11	Anterior wall	Abdomen	Urinary irritation	Abdominal pain
5	10/16/2008	M/64	AC	Well	1.0	30	Back wall	Abdomen	Urinary irritation	Hematuria
6	11/9/2008	M/57	SCC	Poor	3.2	8	Back wall	Abdomen	Hematuria, Urinary irritation	Hematuria
7	7/14/2009	M/63	AC	Well	3.2	14	Anterior wall	Abdomen		
8	10/3/2009	M/63	AC	Well	5.5	12	Anterior wall	Prostate gland		
9	1/3/2010	M/58	AC	Poor	1.5	10	Inferior wall	Abdomen	Hematuria, urinary irritation	Abdominal pain
10	1/24/2010	M/68	AC	Poor	3.8	9	Back wall	Abdomen		
11	2/25/2010	M/66	TCC	Well	2.4	19	Back wall	Prostate gland	Hematuria, abdominal pain	
12	4/21/2010	M/65	TCC	Well	7.8	24	Back wall	Abdomen		
13	5/14/2010	M/39	SCC	Poor	7.6	6	Left wall	Psoas major	Hematuria, urinary irritation, lumbago abdominal pain	Hematuria, urinary irritation
14	5/27/2010	F/54	SCC	Poor	7.2	5	Back wall	Kidney	Hematuria, abdominal pain	Urinary irritation
15	6/14/2010	F/52	SCC	Poor	2.9	6	Back wall	Uterus	Hematuria, abdominal pain, lumbago	Hematuria
16	9/25/2010	M/47	TCC	Well	4.4	27	Inferior wall	Prostate gland	Hematuria, abdominal pain, lumbago	Abdominal pain, lumbago
17	1/6/2010	M/76	TCC	Well	4.0	18	Inferior wall	Liver	Hematuria	Hematuria
18	2/26/2011	M/35	TCC	Poor	5.0	3	Right wall	Abdomen	Hematuria, abdominal pain	Abdominal pain
19	3/13/2011	M/47	TCC	Poor	4.0	3	Left wall	Abdomen		Abdominal pain
20	3/18/2011	M/52	TCC	Well	5.0	16	Right wall	Abdomen	Abdominal pain	
21	5/9/2011	M/46	TCC	Well	2.3	19	Left wall	Abdomen	Abdominal pain	
22	6/18/2011	M/67	TCC	Well	3.4	26	Inferior wall	Abdomen	Hematuria, urinary irritation	Hematuria, abdominal pain
23	9/26/2011	M/64	AC	Well	1.8	15	Back wall	Abdomen		Hematuria

Note: AC, adenocarcinoma; SCC, squamous cell carcinoma; TCC, transitional cell carcinoma.

sum test was conducted on pre- and post-cryosurgery findings to determine differences in the presence of bladder cancer complications. B mode ultrasound was performed within 3 days after cryosurgery to evaluate pelvic effusion, which reflects the presence of bladder perforation. Follow-up dynamic CT was performed at 1 month intervals. The revised Response Evaluation Criteria in Solid Tumors v1.1 were used to assess the response to treatment of the bladder tumors [4]. Three diagnostic radiologists reviewed CT scans for every case to determine whether progression or recurrence had occurred. Progression-free survival (PFS) was calculated from the date of cryosurgery. The effects on PFS of tumor location and pathologic type were analyzed using Bonferroni's multiple comparison tests, the effect on PFS of the degree of tumor differentiation was evaluated by Kaplan–Meier analysis with the log-rank test and the correlation between PFS and tumor longest diameter was analyzed by linear regression. Statistical differences were indicated by $P < 0.05$, $P < 0.01$ or $P < 0.001$. All analyses were conducted using GraphPad software (San Diego, CA, USA).

Results

Clinical data

Data for all 23 patients are shown in Table 1. Eleven patients were from China, eight from Southeast Asia and four from the Middle East. All had been diagnosed with metastatic bladder cancer in other centers and came to our hospital for cryosurgery. There were 21 males and two females and their age ranged from 35 to 76 years, with a mean of 58 years. Tumors were located in the anterior wall, right or left wall, back wall or inferior wall of the bladder in four, six, nine and four cases, respectively. Six tumors were adenocarcinomas (AC), six were squamous cell carcinomas (SCC) and 11 were transitional cell carcinomas (TCC). Thirteen tumors were well differentiated and 10 were poorly differentiated. In the process of follow-up examination, all patients have abandoned freezing treatment again.

Perioperative outcomes

In all of the patients in this study, the tumor had penetrated the bladder wall. Due to the flexibility and resilience of the bladder, we consider only the form of the tumor in treatment, regardless of the shape of the bladder wall. All cryosurgical procedures were performed successfully and there were no treatment-related deaths or conversions to chemotherapy. There were minor complications but no major complications of the treatment. Symptoms of bladder cancer present before and within 3 days after percutaneous cryoablation are shown in Table 2. These new treatment-related symptoms are not considered as complications and no other minor or

Table 2
Clinical findings in 23 patients who underwent cryotherapy.

Symptoms	Before cryosurgery, no. of patients (%)	After cryosurgery, no. of patients (%)	*P* Value
Hematuria	13 (57)	10 (43)	<0.05
Urinary irritation	7 (30)	2 (9)	<0.001
Hypogastralgia	9 (39)	6 (26)	<0.05
Lumbago	2 (9)	1 (4)	<0.05

Note: Measurements were made before and within 3 days and compared using the Wilcoxon matched pairs signed rank sum test.

severe complications were noticed. All complications had disappeared completely after 2 weeks.

PFS after cryosurgery

The PFS of the 23 patients who underwent cryosurgery for bladder cancer was 14 ± 8 months. PFS was 12 ± 1 months in those with tumors in the anterior wall of the bladder, 11 ± 7 months for the right or left wall, 15 ± 9 months for the back wall and 20 ± 8 months for the inferior wall; these differences in PFS were not statistically significant (Fig. 2A). The PFS of patients with SCC (8 ± 3 months, Fig. 2B) was shorter than that of patients with AC (15 ± 8 months, $P < 0.05$) or TCC (17 ± 8 months, $P < 0.05$). The PFS of patients with well differentiated tumors (20 ± 6 months, Fig. 2C) was significantly longer than that of those with poorly differentiated tumors (7 ± 3 months, $P < 0.0001$). PFS was negatively correlated with tumor longest diameter ($P = 0.0235$, $r = -0.47$, Fig. 2D).

Discussion

In patients with metastatic disease, systemic chemotherapy is the only treatment that has been shown to improve survival. In a randomized phase III trial in advanced bladder cancer, Loehrer et al. (1990) reported an M-VAC regimen (cisplatin, methotrexate, doxorubicin, vinblastine) to be significantly superior to cisplatin monotherapy in terms of objective response rate (39% vs 12%), PFS (10 vs 4.3 months, and overall survival (12.5 vs 8.2 months) [8]. Radiation appeared to be as effective as intravesicular chemotherapy [12]. The additional use of targeted therapies has failed to demonstrate benefit in second line treatment to date [1]. Because systemic chemotherapy may have severe side effects, such as significant hematologic or mucosal toxicity, or lead to treatment-related death [19], some patients with metastatic bladder cancer refuse this treatment. Percutaneous cryoablation may be an attractive alternative treatment for metastatic bladder cancer. In the present retrospective study, 4 years of follow-up data from 23 patients obtained from our hospital's database were analyzed to determine the safety and efficacy of this procedure.

All cryosurgical procedures for bladder cancer were performed successfully, with no treatment-related deaths. Hematuria, urinary irritation, hypogastralgia and lumbago improved within 3 days after percutaneous cryoablation and all complications had disappeared completely after 2 weeks. No cases of bladder perforation or sexual dysfunction were observed in this study, though we cannot say that these will never occur. Bladder cancer often infiltrates

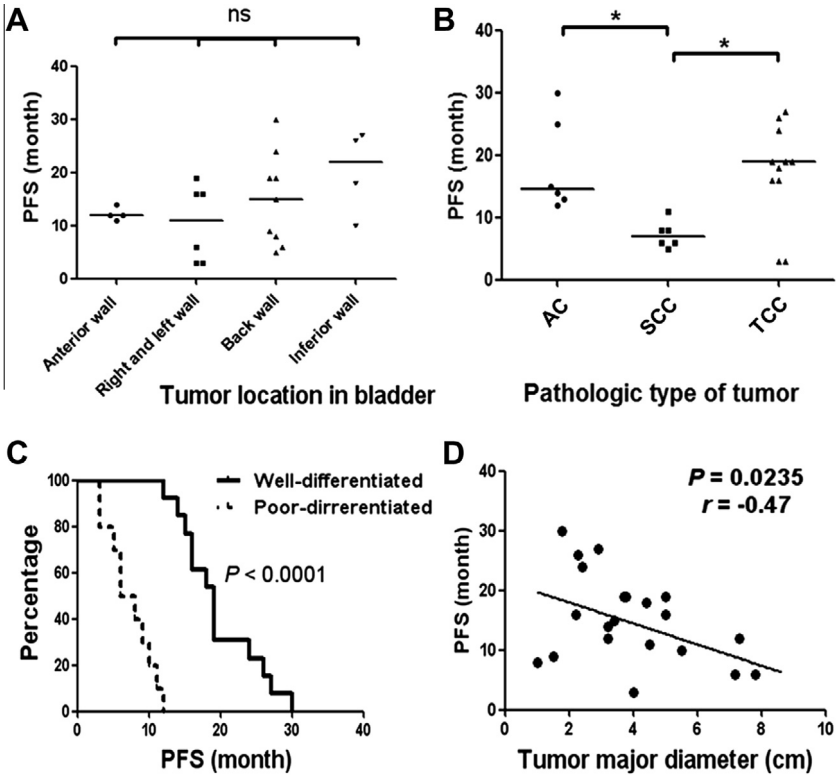

Fig. 2. Effect of tumor characteristics on progression-free survival (PFS). For location (A) and pathologic type (B), Bonferroni's multiple comparison test was used. AC, adenocarcinoma; SCC, squamous cell carcinoma; TCC, transitional cell carcinoma. Horizontal lines in the scatter dot plots represent the median. ns, no statistical difference; *$P < 0.05$. For differentiation status (C), the log-rank test was used. Tumor longest diameter and PFS (D) were correlated by linear regression.

visceral organs, and injury to the ureter, urethra, prostate, vagina, uterus or bowel by ice ball formation could have severe consequences. In the present study, all tumors had penetrated the bladder wall and only palliative treatment by percutaneous cryoablation was conducted. Ice ball formation was well monitored to avoid any injury to other tissues, it is hard to believe that never dissection was needed.

The therapeutic effect of percutaneous cryoablation was evaluated by means of PFS. The PFS of the 23 patients who underwent comprehensive cryosurgery for metastatic bladder cancer was 14 ± 8 months, which was better than that reported for cisplatin monotherapy and M-VAC combination chemotherapy [8]. On the premise of effective control of tumor growth, cryosurgery could have some advantages in the preservation of immune function, it has yet to be further research. Because tumor number, size, location, differentiation status and histopathology may influence the therapeutic effect of cryosurgery [13], the associations between the effect of percutaneous cryoablation and these factors were investigated. The PFS of patients with SCC (8 ± 3 months) was shorter than that of those with AC (15 ± 8 months, $P < 0.05$) or TCC (17 ± 8 months, $P < 0.05$) and the PFS for well differentiated tumors (20 ± 6 months) was significantly longer than that for poorly differentiated tumors (7 ± 3 months, $P < 0.0001$). PFS was negatively correlated with tumor longest diameter ($P = 0.0235$, $r = -0.47$). For metastatic tumor, recurrence is hard to avoid, so inherent biological behaviour and malignant degree will determine the rate of recurrence and disease progression. Observed from our data, SCC, poorly differentiated tumors and big tumor volume were all factors associated with poor prognosis.

In conclusion, percutaneous cryoablation may be an option in the treatment of metastatic bladder cancer. The side effects were relatively mild and a PFS of 1 year can be achieved. A larger number of cases is required, however, and long term survival following this therapy and its role in combination with other therapies awaits further research.

References

[1] J. Bellmunt, D.P. Petrylak, New therapeutic challenges in advanced bladder cancer, Semin. Oncol. 39 (2012) 598–607.

[2] J. Chen, B. Liang, Y. Yuan, C. Liu, L. Li, H. Li, F. Mu, J. Zuo, K. Xu, Comprehensive treatment of malignant mesothelioma patients after the failure of systemic chemotherapy, Cryobiology 65 (2012) 284–288.

[3] J.B. Chen, J.L. Li, L.H. He, W.Q. Liu, F. Yao, J.Y. Zeng, Y. Zhang, K.Q. Xu, L.Z. Niu, J.S. Zuo, K.C. Xu, Radical treatment of stage IV pancreatic cancer by the combination of cryosurgery and iodine-125 seed implantation, World J. Gastroenterol. 18 (2012) 7056–7062.

[4] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij, New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2009) 228–247.

[5] S.N. Goldberg, C.J. Grassi, J.F. Cardella, J.W. Charboneau, G.D. Dodd 3rd, D.E. Dupuy, D. Gervais, A.R. Gillams, R.A. Kane, F.T. Lee Jr., T. Livraghi, J. McGahan, D.A. Phillips, H. Rhim, S.G. Silverman, Image-guided tumor ablation: standardization of terminology and reporting criteria, J. Vasc. Interv. Radiol. 16 (2005) 765–778.

[6] J. Li, J. Chen, L. Zhou, J. Zeng, F. Yao, B. Wu, G. Fang, C. Deng, Z. Chen, Y. Leng, K. Xu, L. Niu, J. Zuo, Comparison of dual- and triple-freeze protocols for hepatic cryoablation in a Tibet pig model, Cryobiology 65 (2012) 68–71.

[7] P.J. Littrup, A. Mody, R. Sparschu, P. Prchevski, J. Montie, A.P. Zingas, D. Grignon, Prostatic cryotherapy: ultrasonographic and pathologic correlation in the canine model, Urology 44 (1994) 175–183 (discussion 183–174).

[8] P.J. Loehrer Sr., L.H. Einhorn, P.J. Elson, E.D. Crawford, P. Kuebler, I. Tannock, D. Raghavan, R. Stuart-Harris, M.F. Sarosdy, B.A. Lowe, et al., A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study, J. Clin. Oncol. 10 (1992) 1066–1073.

[9] C. Logan, M. Brown, D. Hayne, Intravesical therapies for bladder cancer – indications and limitations, BJU Int. 110 (Suppl. 4) (2012) 12–21.

[10] D.J. Mc, C.B. Taylor, N.J. Heckel, Rapid freezing of the bladder: an experimental and clinical study, J. Urol. 64 (1950) 326–337.

[11] F. Mu, L. Niu, H. Li, M. Liao, L. Li, C. Liu, J. Chen, J. Li, J. Zuo, K. Xu, Percutaneous comprehensive cryoablation for metastatic hepatocellular cancer, Cryobiology 66 (2013) 76–80.

[12] P.F. Mulders, W.J. Hoekstra, R.P. Heybroek, E.R. Schapers, A.L. Verbeek, G.O. Oosterhof, F.M. Debruyne, Prognosis and treatment of T1G3 bladder tumours. A prognostic factor analysis of 121 patients. Dutch South Eastern Bladder Cancer Study Group, Eur. J. Cancer 30A (1994) 914–917.

[13] V.H. Nargund, C.K. Tanabalan, M.N. Kabir, Management of non-muscle-invasive (superficial) bladder cancer, Semin. Oncol. 39 (2012) 559–572.

[14] L. Niu, J. Li, J. Chen, L. Zhou, B. Wu, J. Zeng, G. Fang, C. Deng, F. Yao, Z. Chen, Y. Leng, M. Deng, B. Zhang, M. Liao, K. Xu, J. Zuo, Comparison of dual- and triple-freeze protocols for pulmonary cryoablation in a Tibet pig model, Cryobiology 64 (2012) 245–249.

[15] L. Niu, F. Mu, C. Zhang, Y. Li, W. Liu, F. Jiang, L. Li, C. Liu, J. Zeng, F. Yao, J. Chen, J. Li, J. Zuo, K. Xu, Cryotherapy protocols for metastatic breast cancer after failure of radical surgery, Cryobiology (2013).

[16] J.R. Oddens, A.P. van der Meijden, R. Sylvester, One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe?, Eur Urol. 46 (2004) 336–338.

[17] S. Permpongkosol, T.L. Nicol, L.R. Kavoussi, T.W. Jarrett, Percutaneous bladder cryoablation in porcine model, J. Endourol. 20 (2006) 991–995.

[18] R. Siegel, D. Naishadham, A. Jemal, Cancer Statistics, CA Cancer J. Clin. 63 (2013) (2013) 11–30.

[19] H. von der Maase, S.W. Hansen, J.T. Roberts, L. Dogliotti, T. Oliver, M.J. Moore, I. Bodrogi, P. Albers, A. Knuth, C.M. Lippert, P. Kerbrat, P. Sanchez Rovira, P. Wersall, S.P. Cleall, D.F. Roychowdhury, I. Tomlin, C.M. Visseren-Grul, P.F. Conte, Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study, J. Clin. Oncol. 18 (2000) 3068–3077.