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Angiogenesis and Lymphangiogenesis in Bladder Cancer

Yasuyoshi Miyata, Hideki Sakai and Shigeru Kanda
Nagasaki University Graduate School of Biomedical Sciences
Japan

1. Introduction

In cancer patients, the majority of deaths occur as a consequence of metastatic diseases. In addition, metastasis is a marker for poor prognosis and low quality of life in many malignancies. Several groups have investigated the mechanism of tumor metastasis. Metastatic lesions are formed through a multi-step complex process and then spread either locally at the site of the primary tumor, or into distant organs through the blood or lymphatic vessels.

Another important feature of cancers is the chaotic behavior of tumor growth and cancer cell cycle progression. To maintain such activities, abundant supply of oxygen and nutrients are necessary. Angiogenesis refers to the formation of new blood vessels and development of new branching vessels from the existing tumor tissue vasculature and this pathological process is important to secure adequate blood supply including oxygen and nutrients to the rapidly dividing malignant cells. In fact, there is a good correlation between tumor growth/cancer cell proliferation and the extent of angiogenesis in almost of all cancers.

While there is abundant information on the mechanisms that are involved in the initiation, regulation and maintenance of angiogenesis in cancer tissue, little is known about the mechanisms involved in the formation of new lymphatic vessels (lymphangiogenesis) in cancers. Furthermore, the current knowledge about cancer dissemination through the lymphatics lacks details about the mode of transport of cancer cells within the lymphatic vessels and the mechanisms involved in their exit and seeding into the distant organs.

In this paper, we review the clinical and pathological significance of angiogenesis and lymphangiogenesis in bladder cancer. In addition, the mechanisms that regulate the formation of new vessels in bladder cancer are discussed. Specifically, we focus on the factors that co-regulate these two different vessels and their potential use as predictive marker of outcome in patients with bladder cancer. In addition, we also discuss the limitation of quantification of these vessels in human tissues.

2. Angiogenesis and lymphangiogenesis

2.1 Angiogenesis in cancer tissues

Angiogenesis is defined as the formation of new blood vessels from pre-existing vasculature, and it is an integrated process of tumor growth, maintenance, and progression in solid tumors (Folkmann, 1992). Angiogenesis is a multistep processes involving changes

in the extracellular matrix, cell proliferation, cell migration, and tube formation. Blood vessel density (BVD), a surrogate marker for angiogenesis, correlates with the malignant potential and poor prognosis of patients with various types of cancers. In addition, anti-angiogenic therapy that targets the tumor vascular supply and pathways of cancer cell dissemination was first introduced in 1971 (Folkman, 1971). Since then, numerous investigators have focused on the mechanisms of angiogenesis, including molecular mechanisms. At present, there is a general agreement that the regulation of tumor angiogenesis depends on a complex mechanism that dynamically balances angiogenic and anti-angiogenic factors. In this regard, these factors are secreted by both tumor cells and stromal cells in complicated systems. To complicate the issue, the mechanisms and pathological roles of these factors vary according to the type of cancer, its malignant potential, and systemic condition.

2.2 Lymphangiogenesis in cancer tissues

In addition to angiogenesis, many investigators have examined the process of lymphangiogenesis, i.e., the formation of new lymphatic vessels, due to its importance in lymph node metastasis and distant metastasis. Lymph node metastasis occurs in various types of malignancies and its presence is considered a strong predictor of recurrence and poor survival of patients with bladder cancer. However, the clinical role and prognostic value of lymphangiogenesis in cancer patients remain unclear, largely due to the lack of specific endothelial markers for lymphatic vessels as well as the lack of proper imaging procedures for lymphatic vessels in human tissues (Pepper, 2001). In recent years, various specific antibodies for lymphatic endothelial cells have been developed and used to investigate the clinical and pathological significance of lymphangiogenesis in cancer patients. Similar to angiogenesis, evidence suggests that lymphangiogenesis is also regulated by complex mechanisms that include a variety of factors. While various common mechanisms regulate the processes of angiogenesis and lymphangiogenesis, other mechanisms vary according to these processes. For example, in contrast to angiogenesis, no intrinsic anti-lymphangiogenic molecules have yet been isolated.

Thus, to discuss the pathological roles, predictive values, and potential therapeutic targets of angiogenesis and lymphangiogenesis, it is important to understand the various complex mechanisms and cooperative functions involved in these two processes.

2.3 Angiogenesis and lymphangiogenesis in bladder cancer

BVD is often used in the analysis of human cancer tissues as a surrogate and semi-quantitative marker of angiogenesis. Previous studies suggested that BVD provides significant information on prognosis and survival in patients with bladder cancer (Streeter & Harris, 2002; Goddard, 2003). However, other investigators were less supportive for the prognostic value of BVD, especially in patients with non-muscle-invasive bladder cancer (NMIBC) (Korkolopoulou, et al., 2001; Ioachim, et al., 2006; Miyata, et al., 2006). Table 1 provides a summary of the currently held opposing views on BVD.

Such discrepancy could be attributed to differences in methodology, such as methods used for counting, size of the field of view, definition of microvessel, and antibodies used in different assays. For example, measurement at periphery or growth from of the tumor (Stavropoulos et al., 2004) or at highest vascularity "hot spots" (Korkolopoulou et al., 2001). Furthermore, the diameter of the microvessel was no mentioned in some studies; though

other provided descriptive terms (the lumen diameter was smaller than approximately eight red blood cells) (Stavropoulos, 2004). More detailed problems are described in the following section.

Patients	Findings	Reference
109 NMIBC	Predictor of muscle invasion in G3 patients, though not an independent factor.	Starvropoulos
66 NMIBC	Independent predictor of recurrence-free survival, particularly in T1G2 tumors	Santos
35 NMIBC + 80 MIBC	Independent predictor for overall survival in MIBC. No significant role in NMIBC	Korkolopoulou
87 NMIBC + MIBC	Independent predictor of lymph node metastasis.	Susuki
104 NMIBC + 22 MIBC	Not significant for recurrence-free, metastasis-free, or cause-specific survival.	Miyata

NMIBC: non-muscle-invasive bladder cancer, MIBC: muscle-invasive bladder cancer

Table 1. Predictive value of blood vessel density (BVD) for progression and survival.

In addition to semi-quantitative measures of BVD, vascular invasion by tumor cells (blood vessel invasion, BVI) has also been identified as a prognostic factor in bladder cancer (Harada et al., 2005). Furthermore, vascular area and various parameters related to the shape, relapse, and/or complexity of the vessels have been suggested as important for more detailed discussion on the relationship between angiogenesis and pathological role, prognosis, and survival. In this regard, several investigators paid special attention to the morphological variability in the vascular pattern (Korkolopoulou et al., 2001; Sharma et al., 2005), and one study reported that the vascular area was an independent predictor of overall survival in patients with T1 disease whereas BVD was not (Korkolopoulou et al., 2001).

In contrast to angiogenesis, there is little or no information on the clinical and pathological significance and predictive value of lymphangiogenesis in patients with bladder cancer. Several studies reported that higher LVD correlates significantly with malignant behavior, cancer cell progression, and prognosis (Fernández et al., 2008; Miyata et al., 2006). In addition, one report indicated that the pathological role of lymphangiogenesis was depended on the location of lymphatic vessels, such as intra-tumoral and peri-tumoral area. In other words, intra-tumoral LVD correlated with histological differentiation, and peri-tumoral LVD correlated with lymph node metastasis (Fernández, et al., 2008). Similar to BVI, of lymphatic vessel invasion (LVI) by tumor cells was also identified as a prognostic factor in bladder cancer (Algaba, 2006). In general, however, information on lymphangiogenesis in human bladder cancer is to a large extent scarce, compared to that on angiogenesis.

2.4 Regulation of angiogenesis and/or lymphangiogenesis

Members of the vascular endothelial growth factor (VEGF) family are the most important molecules involved in the processes of angiogenesis and lymphangiogenesis. This family consists of 7 members, including VEGF-A, -B, -C, -D, and -E, svVEGF, and placental growth factor. In addition, three types of receptors have so far been identified: VEGFR-1, -2, and -3 (Takahashi et al., 2005). The angiopoietin (Ang) family also encompasses several pro-angiogenic factors. This family consists of Ang-1 and -2 and Tie2 tyrosine kinase receptors,

and the system is influenced by VEGF family. In addition, several factors, for example, fibroblast growth factor (FGF)-2, hepatocyte growth factor (HGF), and insulin-like growth factor (IGF), are also reported to be involved in the regulation of both angiogenesis and lymphangiogenesis.

Angiostatin and endostatin, which are both produced by proteolytic cleavage of plasminogen and collagen XVIII, respectively, are well characterized anti-angiogenic factors. (O'Reilly, et al., 1994, 1997). In addition, thrombospondins (TSPs) also inhibits angiogenesis (Lawler, 2000). Another report indicated that down-regulation of TSP-1 secretion in bladder cancer tissues was a key event in the change from an anti-angiogenic to an angiogenic phenotype during carcinogenesis (Campbell, et al., 1998). On the other hand, there are conflicting results on the relationship between TSP-1 expression and BVD in human bladder cancer. Specifically, TSP-1 staining correlated negatively with BVD (Grossdfeld et al., 1997), whereas other investigators reported that TSP-1 expression correlated positively with BVD (Ioachim et al., 2006).

We review here in detail two representative pro-angiogenic factors; VEGF family and Ang family. Their selection was based on the finding that they are potential therapeutic targets in various cancers. Actually, targeted therapies based on these factors have been tested already in patients with bladder cancer. Unfortunately, however, anti-angiogenic factor-targeted therapy is still in its infancy and there is little possibility to use such drugs for treatment of bladder cancer in the near future.

2.5 VEGF family

Among the VEGF family members, VEGF-A is a major regulator of angiogenesis. On the other hand, both VEGF-C and VEGF-D have been found to play major roles in lymphangiogenesis. Furthermore, VEGFR-2 and VEGFR-3 are reported to be the major mediators of angiogenic response in blood endothelial cells and lymphangiogenic response in lymphatic endothelial cells, respectively. In other words, VEGF-A signaling through VEGFR-2 is the major pathway that activates angiogenesis by stimulating cell proliferation, survival, and migration of endothelial cells (Shibuya & Claesson-Welsh, 2006). Furthermore, the VEGF-C/D-VEGFR-3 signaling pathway is important for the growth of lymphatic endothelial cells (Skobe et al. 2001; Stacker et al., 2001; Lin, et al., 2005). In support of this notion, blocking the VEGF-C/D-VEGFR-3 signaling pathway was reported to inhibit tumor lymphangiogenesis and lymph node metastasis in several xenograft and transgenic tumor models (He et al., 2002; Lin et al., 2005; Roberts et al., 2006).

In contrast to the above studies, several groups reported that VEGF-A could stimulate lymphangiogenesis *in vivo* (Nagy et al., 2002; Cursiefen et al., 2004). In addition, in an animal model of chemically-induced skin cancer, VEGF-A induced lymphangiogenesis and promoted lymphatic metastasis (Hirakawa et al., 2005). Conversely, VEGF-C and VEGF-D were reported to play important roles in angiogenesis under various physiological and pathological conditions (Cao 1998, Jussila & Alitalo, 2002).

VEGFR-1 has a high affinity for VEGF-A, VEGF-B, and PIGF. However, its tyrosine kinase activity is comparatively weak (Autiero, et al., 2003; Shibutya & Claesson-Welsh, 2006). VEGFR-1 is expressed in endothelial cells. In addition, it is also expressed in monocytes/macrophages, hemopoietic cells, and pericytes. Its tyrosine kinase activity is required for stimulation of hemopoietic cell migration towards VEGFs and PIGFs (Barleon, et al., 1996; Clauss, et al. 1996). Based on these results, VEGF-B, PIGF, and VEGFR-1 are

thought to play minimal roles in angiogenesis. In fact, they do not activate angiogenesis during development. However, they have been reported to exhibit angiogenic activity under a variety of pathological conditions (Fisher et al., 2008). For examples, in animal experiments, PIGF was associated with angiogenesis in various pathological conditions including ischemia, inflammation, and tumor growth (Carmeliet, et al., 2001; Luttun, et al., 2002).

The role of VEGFR-2 in lymphangiogenesis is still controversial. VEHGR-2 is expressed at low levels in lymph vessels, and VEGF-VEGFR-2 signaling can induce lymphatic vessel formation (Hong et al., 2004). On the other hand, evidence suggests that lymphangiogenesis induced by such system involves the recruitment of immune cells producing VEGF-C and – D (Crusiefen, et al., 2004).

The following schematic diagram illustrates the relationship between VEGFs and VEGFRs and angiogenesis and lymphangiogenesis:
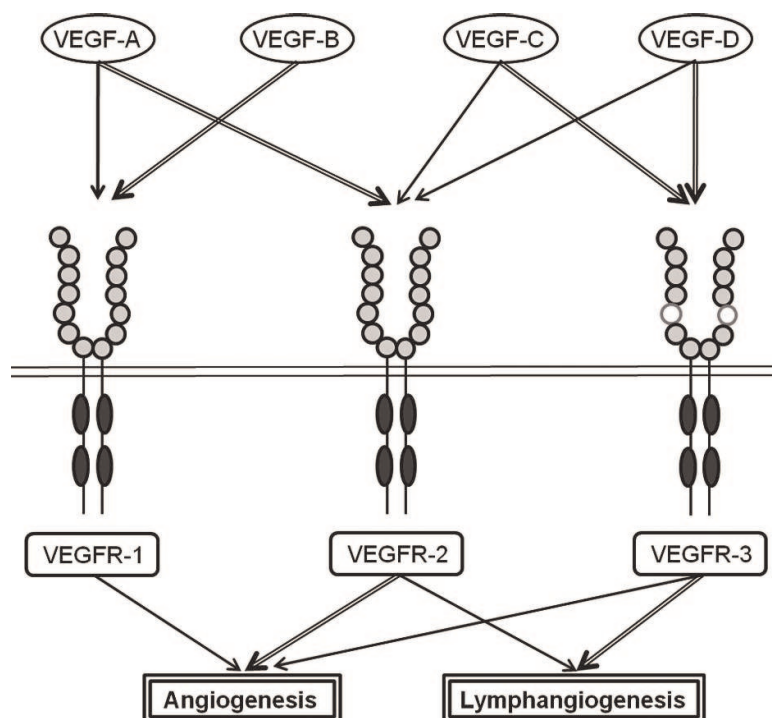
2.6 VEGF family in bladder cancer

Angiogenesis in bladder cancer involves the VEGF-A signaling through the receptor VEGFR-2. The interaction between VEGF-A and VEGFR-2 plays a crucial role in tumor growth, progression, and prognosis via regulation of angiogenesis in patients with bladder cancer.

VEGF-C and –D are highly expressed in cancer cells than in normal urothelial cells (O'Breien, et al., 1995; Zu et al., 2006; Miyata, et al.). Several investigators have reported that the expression of VEGF-C in bladder cancer is closely associated with tumor progression including lymph node metastasis (Suzuki, et al., 2005; Zu, et al., 2006). In addition, the expression of VEGF-C was a significant predictor of poor cause-specific survival in 87 patients. However, multivariate analysis in the same study showed that VEGF-C was not an independent factor and its expression did not correlate with various clinicopathological features (Suzuki, et al, 2005). On the other hand, the same analysis showed that the

expression of VEGF-C in bladder cancer was a significant and independent predictor of pelvic lymph node metastasis. Thus, these reports have demonstrated that VEGF-C plays important role in the malignant aggressiveness and its overexpression is associated with poor prognosis of patients with bladder cancer. On the other hand, controversy exists regarding the prognostic value of VEGF-C expression in bladder cancer (Mylona, et al., 2006).

The fact that VEGF-C binds to and stimulates phosphorylation of tyrosine kinase receptor VEGFR-3 is well-known. In addition to VEGFR-3, VEGF-C also binds and activates VEGFR-2, but not VEGFR-1 (Roberts, et al., 2006). Because VEGFR-2 is the major pathway of angiogenesis, it is possible that VEGF-C also correlates with angiogenesis in bladder cancer. One study of 45 patients with bladder cancer reported that VEGF-C expression did not correlate with microvessel density (Zu, et al., 2006). On the other hand, we found that VEGF-C expression correlated positively with both MVD and LVD in 126 patients with bladder cancer. Another group reported that VEGF-C expression correlated with intra-tumoral BVD, but not with overall BVD. They also showed that VEGF-C expression correlated significantly with both intra-tumoral and peri-tumoral LVD (Afonso, et al., 2009). The reasons for these discrepancies are probably related to differences in antibodies used to measure MVD and also differences in sample size.

VEGF-D expression is also reported to be significantly associated with pathological features and prognosis of patients with bladder cancer (Miyata et al, 2006; Herrmann, et al., 2007). In addition, several studies demonstrated that VEGF-D expression also correlated with tumor growth, metastasis, and survival of patients with bladder cancer (Miyata, et al., 2006; Herrmann, et al, 2007). However, in comparison with VEGF-C, information regarding pathological significance and predictive value of VEGF-D in patients with bladder cancer is very limited.

Similarly, there is a little information on VEGF-B expression in bladder cancer. To our knowledge, there is only one study on VEGF-B m-RNA expression in bladder cancer tissues (Fauconett, et al., 2009). These authors used Northern blot analysis and reported the lack of VEGF-B mRNA expression in 37 bladder cancer specimens.

2.7 Ang family in cancers including bladder cancer

Angiopoietin (Ang)-1 and -2 have angiogenic function acting on Tie2 tyrosine kinase receptors (Maisonpierre, et al., 1997; Papapetropoulos, et al., 1999). Ang-1 is known as stabilizing factor because it helps to maintain and stabilize mature vessels by promoting interactions between endothelial cells and neighboring cells including pericytes and smooth muscle cells (Maisonpierre, et al., 1997; Papapetropoulos, et al., 1999, 2000). In contrast, Ang-2 is known as an antagonist to Ang-1 because it is expressed at sites of vascular remodeling and acts to destabilize vessels (Maisonpierre, et al., 1997). Interestingly, Ang-2 is reported to potentiate angiogenesis in the presence of VEGF, but causes regression of this process in the absence of VEGF (Maisonpierre, et al., 1997; Holash, et al., 1999). Thus, the angiopoietin-Tie2 system, comprising Ang-1, Ang-2, Tie2, and VEGF, seems to be regulated by complex mechanisms.

In bladder cancer, there are conflicting results on the clinical and pathological significance of angiopoietin-Tie2 system. One study demonstrated a significant correlation between Ang-2 protein expression and high stage, high grade tumors, and poor prognosis, whereas Ang-1 protein expression did not show the same trend (Oka, et al., 2005). It also showed that Ang-2

expression was an independent predictor of overall survival in patients with bladder cancer. On the other hand, Ang-2 mRNA expression in early stage superficial carcinomas and low grade tumors was reported to be significantly higher than in advanced stage muscle invasive carcinomas and high grade tumors (Quentin, et al., 2004). In comparison, the same study also reported that Ang-1 mRNA was expressed at significantly low levels in low grade and early stage tumors compared to high grade or advanced stage tumors. Other studies on Ang-1 and Ang-2 demonstrated the presence of significantly higher serum levels of Ang-1 in patients with bladder cancer relative to the control; and conversely, Ang-2 and Tie2 levels were significantly lower. (Szarvas, et al., 2009). The same study also showed that high Tie2 serum level was an independent prognostic factor for metastasis in multivariate analysis model that included tumor grade and stage.

2.8 Limitation of quantification of angiogenesis and lymphangiogenesis

BVD is often used as a quantitative marker of angiogenesis. The method used for quantification was first described after antibodies to factor VIII-related antigen became commercially availability; these antibodies were used to immunohistochemically stain blood vessels. Since then, various immunohistochemical pan-endothelial markers, such as CD31, CD34, von-Willebrand factor, have been used to stain and study blood vessels. CD31, also known as PECAM-1 (Platelet Endothelial Cell Adhesion Molecule-1), is a 130 KDa integral membrane protein, and is expressed constitutively on the surface of adult and embryonic endothelial cells. The CD34 protein is a member of a family of single-pass transmembrane proteins expressed on blood vessel endothelial cells (Nielsen & McNagny, 2008). However, these markers cannot distinguish between small and large blood vessels (Hassan, et al., 2002). On the other hand, CD105, also known as endoglin, is a disulphide-linked, proliferation-associated, hypoxia-inducible homodynamic cell membrane glycoprotein, and is known to be over-expressed in proliferating endothelial cells and is strongly up-regulated in endothelial cells of neoplastic tissues compared with normal cells (Fonasanti, et al., 2002; Minhajat, et al., 2006). Based on these properties, many recent studies have recommended the use of CD105 for evaluation of angiogenesis in tumor tissues because it reflects the dynamic status of tumor-related angiogenesis compared to other pan-endothelial markers (Sharma, et al., 2005). In fact, so far, CD105 antibody was demonstrated to have a greater specificity for tumor vasculature than other pan-endothelial markers, such as CD31, CD34, and Factor VIII in a clinical study of colorectal cancer (Saadi, et al., 2004).

In bladder cancer tissues, several antibodies have been used to evaluate angiogenesis. These include factor VIII (Lianes, et al., 1998; Shirotake, et al., 2011), CD31 (Korkolopoulos, et al., 2001; Afonso, et al., 2009), and CD34 (Shirotake, et al., 2011; Stavropoulos, et al., 2004; Ioachim, et al., 2006); whereas CD105 has rarely been used in bladder cancer tissues.

It is suggested that CD31, CD34, and CD105 are more useful because they efficiently recognize small-caliber vessels that are associated with angiogenesis in bladder cancer than factor VIII (Santos, et al., 2003). However, this study did not discuss the difference between these markers. Thus, to date, there is no ideal antibody to truly reflect the clinical and pathological significance of angiogenesis in bladder cancer. To this effect, some investigators have doubted the pathological significance and predictive value of BVD in patients with bladder cancer (Table 2).

Similar to angiogenesis, there is no ideal antibody that reflects the significance of lymphangiogenesis. In general, three different antibodies such as anti-lymphatic vessel

endothelial hyaluronan receptor (LYVE)-1 (Yang, et al., 2011), anti-VEGFR-3 (Zhou et al., 2011) and anti-D2-40 (Miyata, et al., 2006; Afonso, et al., 2009,) have been used to detect lymphatic vessels. However, detailed information on the differences and characteristics of each of these factors is not available. Further studies are necessary to discuss the methods of quantification and evaluation of lymphangiogenesis in bladder cancer tissues.

	n	Antibody	Progression	Survival	Reference	year
NMIBC	35	CD31	No	No	Korkolopoulou	2001
NMIBC	66	CD31+CD34+FVIII	Yes*	–	Santos	2003
NMIBC	109	CD34	Yes**	–	Stavropoulos	2004
MIBC	109	FVIII	No	No	Linanes	1998
MIBC	80	CD31	Yes	No	Korkolpoulou	2001
Both	113	CD31+CD34	No	Yes	Bochener	1995
Both	148	CD34	No	No	Ioachim	2006
Both	42	CD31+FVIII	–	–	Gehani	2011

NMIBC, non-muscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; FVIII, factor VIII. * In T1/grade 2 patients. ** In grade 3 patients.

Table 2. Prognostic significance of blood vessel density (BVD)

3. Conclusion

Angiogenesis and lymphangiogensis play important roles for tumor growth and progression in bladder cancer. VEGF family and Ang family are well known to be associated with these phenomenon in bladder cancer. However, other factors and molecules are also speculated to regulate them by complex mechanism. So, detailed mechanism of their regulations is still fully understood. In addition, further studies are necessary to discuss the methods of quantification and evaluation of angiogenesis and lymphangiogenesis in bladder cancer tissues.

4. Acknowledgement

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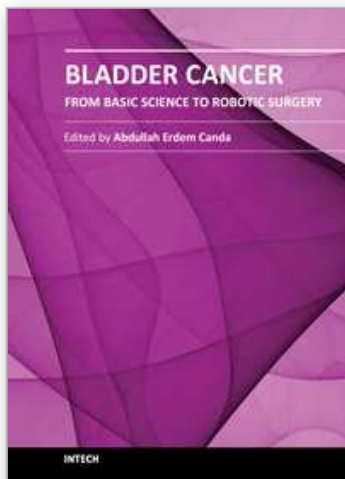
Bladder Cancer - From Basic Science to Robotic Surgery

Edited by Dr. Abdullah Canda

This book is an invaluable source of knowledge on bladder cancer biology, epidemiology, biomarkers, prognostic factors, and clinical presentation and diagnosis. It is also rich with plenty of up-to-date information, in a well-organized and easy to use format, focusing on the treatment of bladder cancer including surgery, chemotherapy, radiation therapy, immunotherapy, and vaccine therapy. These chapters, written by the experts in their fields, include many interesting, demonstrative and colorful pictures, figures, illustrations and tables. Due to its practicality, this book is recommended reading to anyone interested in bladder cancer.

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