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EDITORIAL

Emergence of neural regulatory mechanisms in carcinogenesis

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Abstract

Emerging data indicate that the nervous system plays an important role in carcinogenesis. However, more studies are required to help further elucidate the mechanisms involved in the neural regulation of carcinogenesis. Some recent findings describing the neural regulatory mechanisms of action in prostate cancer, pancreatic cancer and hepatocellular carcinoma are discussed, with a focus on the sympathetic, parasympathetic, and sensory neuronal elements of the nervous system. Norepinephrine, which is released by the sympathetic nervous system and binds to the beta-adrenergic receptor, regulates cellular responses in both normal and tumor cells. It has also been shown that the destruction of sensory neurons can prevent or at least slow pancreatic cancer. Cortisol, the main stress hormone, is also discussed and how it could potentially be involved in hepatocellular carcinoma development. The importance of studying other signaling molecules in the nervous system, such as oxytocin and its receptor, the oxytocin receptor, and how they might be involved in carcinogenesis when aberrantly expressed is highlighted. This is an area of study which clearly needs further investigation. A clearer understanding of the detailed mechanisms of how the nervous system is involved in carcinogenesis could potentially aid in the identification of novel biomarkers and development of novel preventative and therapeutic strategies in various cancers.

Key words: Neural regulation; Prostate; Pancreatic cancer; Hepatocellular carcinoma; Oxytocin; Oxytocin receptor

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Core tip: Increasing evidence points to the importance of neural regulatory mechanisms in carcinogenesis. However, these mechanisms are not fully understood. A better understanding of these mechanisms could lead to prevention, early detection, and novel therapeutic strategies in various cancers. Consequently, this area of study warrants further investigation.

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INTRODUCTION

The nervous system plays an important role in maintaining homeostasis in peripheral organs by facilitating cross-talk between these organs and the brain. Emerging data from several pre-clinical and clinical studies have suggested that this neural regulation is involved in cancer progression and therapeutic resistance in many peripheral organs when it gets altered[1]. Additionally, psychosocial studies indicate that there are alterations observed in brain activities of neuromediators and neuroendocrine hormones in patients with solid tumors[1-3].

The sympathetic and parasympathetic divisions of the autonomic nervous system directly innervate most distal organs and facilitate tissue homeostasis in them by releasing neurotransmitters such as catecholamines and acetylcholine (Ach). Both the sympathetic and parasympathetic divisions of the autonomic nervous system have been shown to regulate tumor cell growth, migration, and invasiveness. When the sympathetic nervous system (SNS), which mediates the flight-or-flight stress responses gets activated, it releases the neurotransmitter, norepinephrine (NE) *via* its nerve fibers[4,5]. NE and cortisol (the major stress hormone) bind to the beta-adrenergic receptor or the intracellular glucocorticoid receptor, respectively, to trigger cellular responses[6]. Cortisol release has been linked to the development and progression of various cancers[7-11]. Ach can bind to nicotinic and muscarinic receptors which are expressed on tumor and stromal cells in the tumor microenvironment[1,12].

While more is known about the emerging role of the nervous system in cancer progression, fewer studies have been done on elucidating its role in cancer initiation.

CURRENT FINDINGS

There is an emerging understanding of the neural regulatory mechanisms in carcinogenesis (Figure 1). Previously, some studies have proposed that solid tumors lacked innervation. However, newer studies have demonstrated the process of neoneurogenesis in which nerves infiltrate solid tumors. Specifically, some studies have shown that nerves play a role in the etiology of prostate, breast, and pancreatic solid tumors[13-15].

Magnon *et al*[13] conducted a study using mouse models and showed that prostate cancer development was regulated by the formation of autonomic nerve fibers in the prostate gland. Prostate cancer development was inhibited by genetic deletion of neurotransmitter activity, stromal b2- and b3-adrenergic receptors. Additionally, in a retrospective blinded study conducted by this group using 43 prostate adenocarcinoma specimens, it was found that the denser the amount of sympathetic and parasympathetic nerve fibers in the tumor microenvironment, the poorer the patient outcomes[13]. The SNS nerve fibers provide NE which acts on b2- and b3-adrenergic receptors (Adrb2, Adrb3) expressed on stromal cells and plays a role in the development and progression of prostate tumors. Additionally, nerve fibers from the parasympathetic nervous system provide tumors with Ach, which promotes prostate tumor growth and metastasis[13].

Previous studies have shown that gastric tumorigenesis is enhanced by activity of the SNS[16-18]. Like the prostate, the pancreas is heavily innervated by the autonomic nervous system. Saloman *et al*[19] have suggested that pancreatic cancer could be prevented or slowed *via* the destruction of some sensory neurons. Sensory neurons

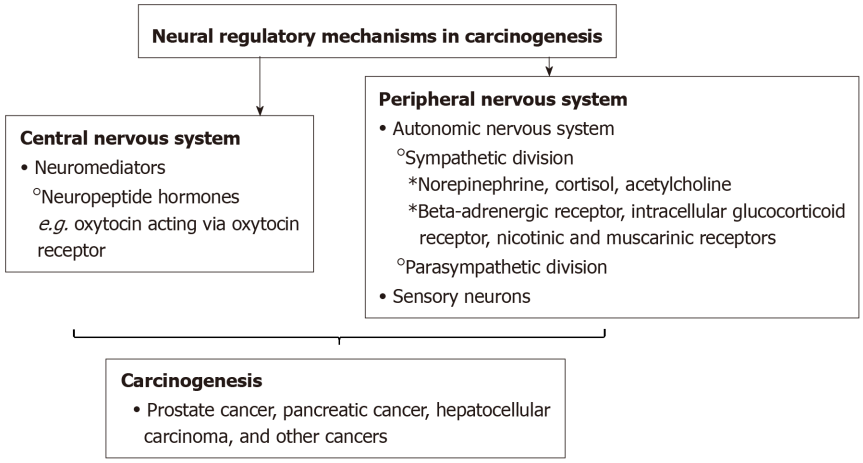

Figure 1 Neural regulatory mechanisms in carcinogenesis.

densely populate pancreatic tumors and the stimulation of these neurons have been shown to advance inflammation[19,20]. Such inflammation is believed to initiate tumors by creating a conducive environment[19,20].

Wu *et al*[11] suggested that cortisol plays a role in hepatobiliary carcinoma (HCC) development. In HCC patients, serum levels of cortisol have been shown to be higher than in healthy individuals. Additionally, HCC cell cultures exposed to cortisol has been shown to repress the expression of p53 by upregulating the expression of Bcl2L12, a suppressor of p53[11].

CONCLUSION

The findings thus far suggest the emergence of a potentially critical role of the nervous system in carcinogenesis. This requires further investigation. It would be interesting to study how other signaling molecules which have traditionally been associated with nervous system function, but recently been implicated in carcinogenesis, play a role in neural regulation in carcinogenesis. For example, many neuropeptides are aberrantly expressed in cancer cells. One recently discovered example is oxytocin. Oxytocin is produced by hypothalamic neurons and has multiple roles in the central nervous system. Apart from its well-known functions in the female reproductive system (milk ejection), oxytocin has more recently been shown to play roles in stress and trust, anxiety, social interaction and bonding, and parental care, as well as on neuropsychiatric disorders linked to such social behaviors[21,22]. Even further, emerging findings are linking the aberrant expression of oxytocin and its receptor, the oxytocin receptor to various cancers[23-27]. A better understanding of the detailed mechanisms of the role nerves and neural mediators play in carcinogenesis, could lead to the identification of novel biomarkers and development of novel preventative, early detection, or therapeutic strategies for various cancers.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic significance of castrate testosterone levels for patients with intermediate and high risk prostate cancer

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Author contributions: Ozyigit G and Akyol F designed research; Ozyigit G, Akyol F and Hurmuz P performed research; Yuce D and Hurmuz P analyzed data; Hurmuz P, Ozyigit G, Yuce D and Akyol F wrote the paper.

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Abstract

BACKGROUND

Testosterone level of < 50 ng/dL has been used to define castrate level after surgery or after androgen deprivation treatment (ADT) in metastatic prostate cancer (PC).

AIM

To evaluate the effect of two different castrate testosterone levels, < 50 and < 20 ng/dL, on biochemical relapse free survival (BRFS) in patients with non-metastatic intermediate and high risk PC receiving definitive radiotherapy (RT) and ADT.

METHODS

Between April 1998 and February 2011; 173 patients with intermediate and high risk disease were treated. Radiotherapy was delivered by either three-dimensional-conformal technique to a total dose of 73.4 Gy at the ICRU reference point or intensity modulated radiotherapy technique to a total dose of 76 Gy. All the patients received 3 mo of neoadjuvant ADT followed by RT and additional 6 mo of ADT. ASTRO Phoenix definition was used to define biochemical relapse.

RESULTS

Median follow up duration was 125 months. Ninety-six patients (56%) had castrate testosterone level < 20 ng/dL and 139 patients (80%) had castrate testosterone level < 50 ng/dL. Both values are valid at predicting BRFS. However, patients with testosterone < 20 ng/dL have significantly better BRFS compared to other groups (P = 0.003). When we compare two values, it was found that using 20 ng/dL is better than 50 ng/dL in predicting the BRFS (AUC = 0.63 *vs* 0.58, respectively).

CONCLUSION

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Castrate testosterone level of less than 20 ng/dL is associated with better BRFS and is better in predicting the BRFS. Further studies using current standard of care of high dose IMRT and longer ADT duration might support these findings.

Key words: Prostate cancer; Androgen deprivation therapy; Radiotherapy; Testosterone; Castration

Core tip: Castrate testosterone level of less than 20 ng/dL achieved after primary radiotherapy plus androgen deprivation treatment for non-metastatic prostate cancer is associated with better biochemical relapse free survival. Testosterone level of < 50 ng/dL has been used to define castrate level after surgery or after androgen deprivation treatment in metastatic prostate cancer (PC). In this study, we evaluated the effect of two different castrate testosterone levels, < 50 and < 20 ng/dL, on biochemical relapse free survival in patients with non-metastatic intermediate and high risk PC receiving definitive modern radiotherapy and androgen deprivation treatment. With a median follow up of 125 mo we found that castrate testosterone level of less than 20 ng/dL achieved after primary radiotherapy plus androgen deprivation treatment was found to be associated with better biochemical relapse free survival.

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INTRODUCTION

The use of androgen deprivation therapy (ADT) in combination with radiotherapy (RT) has been the standard treatment for treatment of patients with localized high-risk prostate cancer based on improvements in cancer-specific (CSS) and overall survival (OS) observed in multiple randomized trials[1-3].

ADT has been accepted as the initial treatment for patients with metastatic prostate cancer or when there is elevated serum prostate-specific antigen (PSA) level during the course of disease. Surgical (bilateral orchiectomy) or medical castration [using either a gonadotropin-releasing hormone (GnRH) agonist or a GnRH antagonist ± antiandrogens] are the two methods used for this purpose. Surgical castration was considered to be the primary and a fast cost-effective modality for androgen deprivation that leads to a considerable irreversible decline in serum testosterone to the "castrate level". Medical castration which is reversible through cessation of treatment can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of androgens at the receptor level.

Commonly used castration level of < 50 ng/dL (1.7 nmol/L) was defined more than 40 years ago after surgery, when testosterone measurement techniques were limited[4].This value has been also used after ADT to define castrate level in metastatic prostate cancer[5,6]. However it was shown that the introduction of chemiluminescent immunoassays provided more accurate and sensitive method to determine serum testosterone level[7]. Oefelein *et al*[8] reported that with the use of chemiluminescent assay mean testosterone level was < 15 ng/dL after surgical castration. Thus, using contemporary techniques castrate testosterone level was proposed to be less than 20 ng/dL (0.7 nmol/L).

Although this new cut-off value shows better results compared to 50 ng/dL currently the accepted serum castrate testosterone level is still < 50 ng/dL[9,10]. In this study we evaluated the effect of two different castrate testosterone levels, < 50 and < 20 ng/dL, on treatment outcomes in patients with non-metastatic intermediate and high risk prostate cancers receiving definitive RT and ADT. This is the first study to evaluate the castrate levels on biochemical relapse free survival (BRFS) for non-metastatic prostate cancer patients.

MATERIALS AND METHODS

Patient characteristics

We have a prospective treatment protocol for the definitive treatment of prostate adenocarcinoma patients which was approved by the institutional ethical review board. Details of the protocol was described and published before[11]. In this study we included subset of patients with intermediate and high risk disease according to D'Amico risk group stratification treated between April 1998 and February 2011. Intermediate risk group was defined as Gleason score (GS) of 7, pretreatment prostate-specific antigen (iPSA) > 10 to 20 ng/mL, and stage T1-T2 disease. High risk group was defined as disease with extracapsular extension (stage T3a-b), PSA > 20 ng/mL or GS above 7. Between April 1998 and February 2011 173 patients with median age of 69 (range, 50-82 years) were treated according to the treatment protocol.

Radiotherapy

Radiotherapy was delivered by either three dimensional conformal technique (3DCRT) before March 2009 or intensity modulated radiotherapy technique (IMRT) to a total dose of 76 Gy after March 2009 with daily fraction dose of 2 Gy. Clinical target volume (CTV) was prostate and seminal vesicles for 3DCRT. Seven 6 MV photon beams (anterior, right and left lateral, right and left anterior oblique, right and left posterior oblique) which were equally weighted were used. ICRU reference point (isocenter) dose was 73.6 Gy. For IMRT; CTV was prostate plus proximal seminal vesicle, but in case of extracapsular invasion whole seminal vesicles were included in the field. For planning target volume 5 mm is given in all directions except the rectal side where 3 mm is given. All of the patients receiving IMRT had 3 fiducials implanted to prostate one week before the planning computerized tomography and are used for image guided radiotherapy.

Androgen deprivation therapy and definition of castrate testosterone level

According to institutional treatment protocol all patients received 3 mo of neoadjuvant ADT followed by radiotherapy and additional 6 mo of ADT. ADT was delivered in the form of total androgen blockade (TAB): GnRH agonist (triptoreline, leuprolide, goserelin) plus antiandrogen (cyproterone acetate or bicalutamide). Testosterone levels were measured at each clinical follow-up visits at a single laboratory using immunoassay method (Immulite 2000, Simens, United States). The testosterone level measured during ADT was used as castrate testosterone level either at the 3rd or 6th months after radiotherapy, since all patients were on active adjuvant hormonal treatment during those periods. Patients were considered as having castrate level of testosterone if both measurements taken at the 3rd or 6th month of follow-up after RT were under desired value of 20 ng/dL or 50 ng/dL depending on subset analysis. Threshold value for testosterone recovery time was calculated from the first measurement of testosterone to the date when it is above 50 ng/dL.

Follow up

Patients were seen in every 3 mo for the first 2 years, 4 months for the 3rd and 4th year every 6 mo thereafter. In each visit, total serum PSA, free PSA and total testosterone levels were measured. ASTRO Phoenix definition (nadir PSA+2 ng/dL) was used to define biochemical relapse.

Statistical analysis

SPSS 21.0 (IBM Inc., Armonk, NY, United States) version was used for the statistical analysis. The value of $P < 0.05$ was used to determine statistical significance. Time to last follow-up and biochemical failure was calculated starting from the final date of RT. Kaplan-Meier test was used to estimate survival probabilities and Cox regression was used for hazard rates. Receiver operating characteristic curve (ROC) analyses was used to compare two cutoff values on BRFS.

RESULTS

Median follow up duration was 125 mo (10.4 years). Median initial PSA level was 14.2 ng/dL (range, 2-100 ng/dL) and median Gleason score was 7 (range, 3-9). The clinical and treatment characteristics of the patients are shown in Table 1. All patients received 9 months of planned ADT. Ninety-six patients (56%) had castrate testosterone level of < 20 ng/dL and 139 patients (80%) had castrate testosterone level < 50 ng/dL. Median testosterone recovery time after TAB cessation was 6 months (range, 6-30 mo).

Table 1 The clinical and treatment characteristics of the patients (*n* = 173)

Characteristics	*n* (%)
AJCC 2010 T stage	
T1	3 (2)
T2a	74 (43)
T2b	14 (8)
T2c	16 (9)
T3a	49 (28)
T3b	17 (10)
Gleason score (median)	7 (3-9)
Initial PSA (median)	14 ng/dL (2-100 ng/dL)
D'Amico risk group	
Intermediate	52 (30)
High	121 (70)
Perineural invasion	
Absent	103 (60)
Present	56 (32)
Unknown	14 (8)
Percent positive core biopsy percentage	
≤ 50 %	76 (44)
> 50%	59 (34)
Unknown	38 (22)
Radiotherapy dose	
736 Gy	145 (84)
76 Gy	16 (16)

T: Tumor.

Biochemical relapse free survival

When castrate testosterone level of < 20 ng/dL is used 5 and 10 years BRFS rates were 90% and 83%, respectively (P = 0.001) (Figure 1). Patients with castrate testosterone < 50 ng/dL have 5 and 10 year BRFS rates of 86% and 76%, respectively (P = 0.006) (Figure 2). Thus, both cutoff values are valid at predicting BRFS.

Patients with castrate testosterone value < 20 ng/dL have significantly better BRFS compared to other patient groups (P = 0.003). Figure 3 shows patients with castrate testosterone value of > 50 ng/dL have better BRFS in the first five year compared to patients with castrate testosterone value between 20-50 ng/dL. However, in long term patients with testosterone 20-50 ng/dL have better BRFS than patients with BRFS > 50 ng/dL. Thus, it seems that using cutoff castrate testosterone value of < 20 ng/dL has better predictive value for estimation of BRFS in the follow up.

Multivariate analysis for independent predictors of BRFS was presented in Table 2. Accordingly, BFFS was found to be independent from the baseline patient characteristics including D'Amico risk group, AJCC 2010 tumor stage, and Gleason Score and LHRH type.

When we compare two cutoff values using receiver operating characteristic curve (ROC) analyses, it was found that using 20 ng/dL is better than 50 ng/dL in predicting the BRFS (AUC = 0.63 *vs* 0.58, respectively) (Figure 4, Table 3).

DISCUSSION

Testosterone is known to promote the growth of prostate cancer cells, thus reducing circulating testosterone to castrate levels is the primary aim of treatment in advanced prostate cancer[4]. Historically, the recommended castrate threshold was below 50 ng/dL, and this value is still used in guidelines and clinical trials[5]. However, recent studies show better outcomes when threshold was below 20 ng/dL and the optimum serum castrate levels of testosterone to be achieved with ADT are still debated[8]. In this study we evaluated the effect of use of two different cutoff values on BRFS for patients with intermediate and high risk prostate cancer treated with modern RT

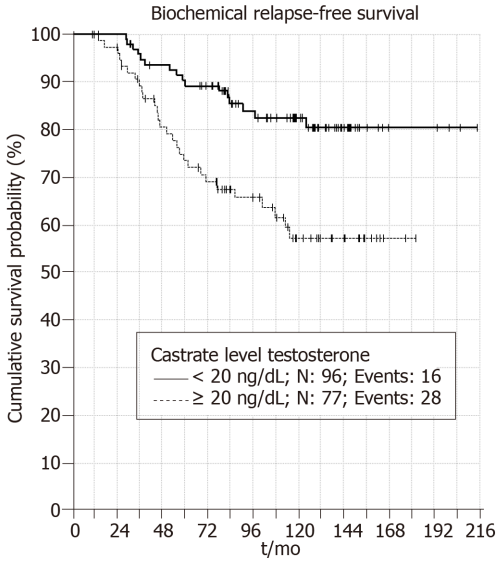

Figure 1 Five and 10 years biochemical relapse free survival rates when castrate testosterone level of < 20 ng/dL is used (*P* = 0.001).

techniques plus ADT. We found that using 20 ng/dL is better than 50 ng/dL in predicting the BRFS. To the best of our knowledge, current study is the first demonstrating the prognostic significance of castrate testosterone level in non-metastatic prostate cancer patients receiving radiotherapy and hormonal treatment with the longest follow up period.

There are some studies that have reported metastatic prostate cancer patients undergoing ADT have superior survival and time to progression if lower castrate levels of testosterone (20 ng/dL) are achieved[9,12,13]. Perachino *et al*[12] retrospectively reviewed 129 patients with a metastatic bony-only prostate cancer previously untreated with ADT who received 3 months of goserelin. With a mean follow-up of 47.5 mo, the risk of death was significantly correlated with Gleason score, 6-month PSA level and the 6th month serum testosterone level. It was concluded that lowering the testosterone level as much as possible should be the goal of ADT in patients with metastatic prostate cancer. Bertaglia *et al*[13] assessed the relationship between serum testosterone levels after 6 months of ADT and treatment outcomes in 153 patients (54 with metastatic disease and 99 with biochemical failure) with prostate cancer. They showed that testosterone levels < 50 ng/dL failed to be associated with time to treatment failure and overall survival. However, a cutoff of < 20 ng/dL was associated with a nonsignificant lower risk of progression and a significant lower risk of death. Using ROC analyses it was concluded that testosterone value of 30 ng/dL offered the best overall sensitivity and specificity for prediction of death. However, these studies are retrospective studies included mixed population of patients with either metastatic/recurrent disease or non-metastatic disease but not receiving local RT.

However current literature seeking for the answer of the same question for non-metastatic disease is small and heterogeneous. PR-7 trial randomly assigned patients having biochemical failure after radiation therapy or surgery plus radiation therapy to continuous or intermittent ADT. Klotz *et al*[14] evaluated the relationship between testosterone levels and cause-specific survival (CSS) and time to androgen-independent progression in 626 patients of the continuous ADT arm of the PR-7 trial. It was concluded that nadir serum testosterone less than 20 ng/dL within the first year of ADT correlates with better CSS and duration of response to ADT in men being treated for biochemical failure undergoing continuous ADT.

A recent study by Bryant *et al*[15] examined the association of sub-castrate testosterone nadir with PSA response and long-term clinical outcomes in 764 US veterans with intermediate or high-risk localized prostate cancer treated with ADT and definitive radiotherapy from 2000-2015. Patients were categorized into testosterone nadir groups based on the minimum testosterone measurement during continuous ADT (< 20 ng/dL *vs* 20-49 ng/dL). With a median follow up of 5 years the results showed that compared to the < 20 ng/dL group, the 20-49 ng/dL group showed higher 10-year biochemical recurrence rates (28.1% *vs* 18.3%, *P* = 0.016) and metastasis rates (12.9% *vs* 7.8%, *P* = 0.01).

On the contrary, Nabid *et al*[16] evaluated the testosterone level at the end of ADT to

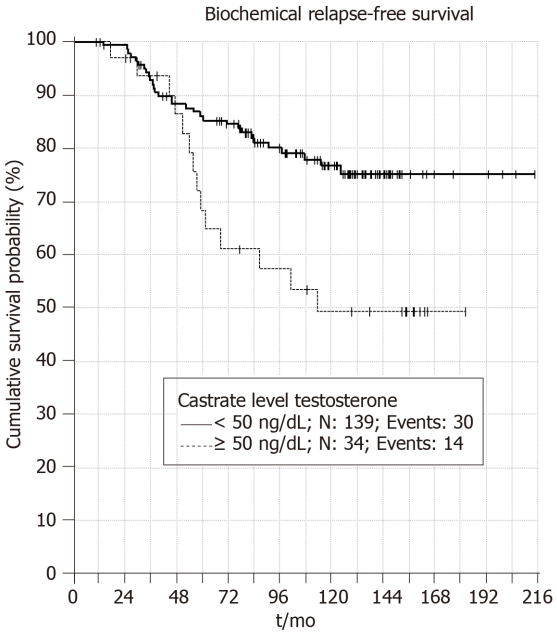

Figure 2 Five and 10 years biochemical relapse free survival rates when castrate testosterone level of < 50 ng/dL is used (*P* = 0.006).

predict the treatment outcomes in intermediate and high risk prostate cancer based on the data of 796 from two randomized trials (PCS III ClinicalTrials.gov, No. NCT00223145 and PCS IV, ClinicalTrials.gov, No. NCT00223171). All patients received ADT and definitive RT. Castration was defined as testosterone level below 1.7 nmol/L (50 ng/dL) and outcomes were compared between the 3 groups; ≤ 0.7 nmol/L, 0.7-1.7, ≥ 1.7 nmol/mL. The results were presented in abstract form. With a median follow up of 9 years the results revealed no difference in treatment outcomes between the groups.

Comparison of current study with the similar studies are shown in Table 4. Duration of hormonal treatment and the RT dose might be the limitations of the study. Institutional treatment protocol included patients prospectively starting from 1998 thus most of the patients received 3DCRT. However, the dose at the ICRU reference point is still 73.6 Gy. The cohort in this study received 9 months of ADT in the form of total androgen blockade. It is known that after GnRH analogues testosterone 95% of testosterone production is eliminated. Adding anti androgens to GnRH in metastatic disease showed improved survival in metastatic prostate cancer but its role in non-metastatic cases are still debatable due to the side effects of the treatment[17,18]. At the beginning of our study in 1998, the long-term results of RTOG 92-02 and EORTC-22961 were not available. Therefore, ADT duration had been planned as 9 months. We revised ADT duration to 2 years and continue with GnRH analogues only after initial 28 d of antiandrogens in our institutional protocol after the final results of RTOG-9202 and EORTC-22961[19,20].

In current study serum testosterone was measured using modern immunoassay method. With a median follow up time of 125 mo, our treatment outcomes are in consistent with the literature supporting the use of lower castrate testosterone level. It seems that lowering testosterone levels below 20 ng/dL should be achieved for better treatment results. This might be achieved either by using long term ADT, TAB or novel antiandrogen treatments. Compared to similar studies previously described our patient have a homogenous treatment protocol and follow up duration is longer. All of the patients were treated according to our institutional treatment protocol and all received the planned treatment. Radiotherapy techniques and fields are described in detail compared to studies described above that has no irradiation data. All the follow ups were carried out at a single center using the same lab. Thus our patients seem to have more homogenous treatment and follow up.

In conclusion, we demonstrated that castrate testosterone level of less than 20 ng/dl achieved after primary RT plus ADT is associated with better BRFS. Using castrate cut off value of 20 ng/dL is better in estimating the BRFS compared to 50 ng/dL. Further studies using current standard of care of high dose IMRT and longer ADT duration might support these findings.

Table 2 Multivariate analysis for independent predictors of biochemical failure free survival

	P value	HR	95%CI for HR	
			Lower	Upper
LHRHa type	0.757	0.0	0.0	1.24E+19
D'Amico risk group (ref: intermediate)	0.397	1.5	0.6	3.89E+00
AJCC 2010 T stage (ref: T1)	0.953			
T2a	0.909	2869.3	0.0	2.85E+62
T2b	0.915	1646.5	0.0	1.64E+62
T2c	0.912	2150.3	0.0	2.14E+62
T3a	0.91	2583.9	0.0	2.57E+62
T3b	0.908	3108.0	0.0	3.10E+62
Gleason score (ref: ≤ 6)	0.799			
7	0.932	1.0	0.5	1.99E+00
≥ 8	0.564	1.3	0.6	2.71E+00

LHRHa: Luteinizing Hormone-Releasing Hormone analog; AJCC: American Joint Committee on Cancer; T: Tumor.

Table 3 Receiver operating characteristic curve analysis for two cut-off values of castrate testosterone levels

	AUC	SE	*P* value	Sensitivity	Specificity
Castrate level testosteron (≤ 20)	0.628	0.049	0.011	63.6%	62.0%
Castrate level testosteron (< 50)	0.582	0.052	0.107	31.8%	84.5%

AUC: Area under curve.

Table 4 Comparison of studies analyzing the effect of castrate testosterone levels in intermediate and high risk prostate cancer patients receiving androgen deprivation treatment and definitive radiotherapy

	Bryant *et al*[15]	Nabid *et al*[16]	Current study
Time	2000-2015	2000-2010	1998-2011
Patient number	764	796	173
Hormone treatment	ADT+/- AA	ADT+/- AA	ADT+AA
Follow up (yr)	5.27	9.15	10.4
RT dose	Unknown	Unknown	73.4-76 Gy
RT technique	Unknown	Unknown	3DCRT-IMRT
Biochemical relapse rate			
< 20 ng/dL	18.3% (10 yr)	20.8%	17% (10 year)
20-49 ng/dL	28.1% (10 yr)	24.9%	35% (10 year)

ADT: Androgen deprivation treatment; AA: Antiandrogen; RT: Radiotherapy; 3DCRT: 3 dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy.

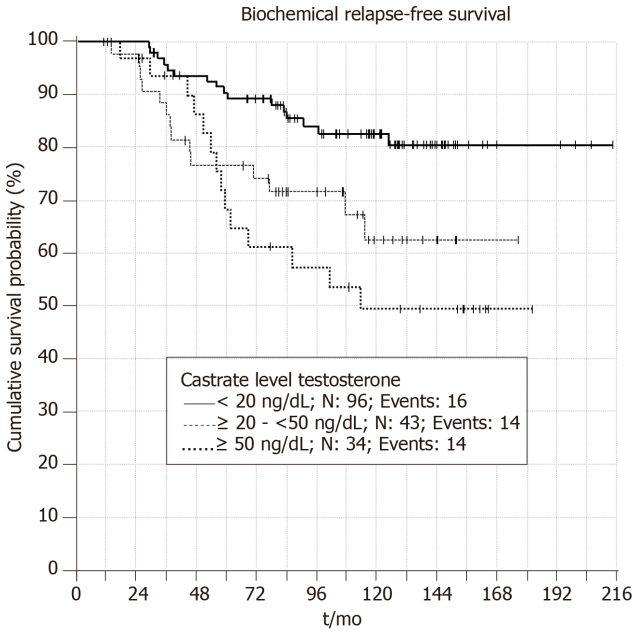

Figure 3 Biochemical relapse free survival rates for patients with different castrate testosterone cut-off values (*P* = 0.003).

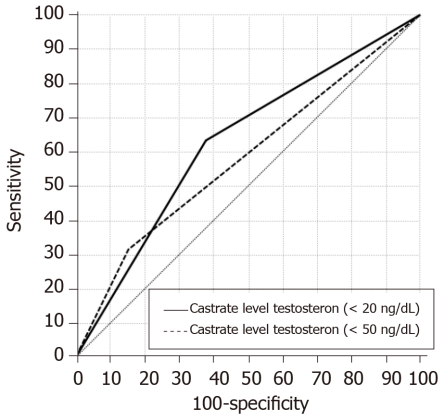

Figure 4 Receiver operating characteristic curve analyses comparing 2 cut-off castrate testosterone values.

ARTICLE HIGHLIGHTS

Research background

Historically, testosterone level of < 50 ng/dL has been used to define castrate level after surgery or after androgen deprivation treatment in metastatic prostate cancer (PC). However, recent studies show better outcomes when threshold was below 20 ng/dL. In this study we evaluate the effect of two different castrate testosterone levels on biochemical relapse free survival in patients with non-metastatic intermediate and high risk PC receiving definitive modern radiotherapy and androgen deprivation treatment.

Research motivation

Current literature seeking for the answer of the castrate testosterone level question for non-metastatic disease is small and heterogeneous.

Research objectives

The aim of the study was to evaluate the effect of two different castrate testosterone levels, < 50 and < 20 ng/dL, on treatment outcomes in patients with non-metastatic intermediate and high risk prostate cancers receiving definitive RT and ADT. This is the first study to evaluate the castrate levels on biochemical relapse free survival for non-metastatic prostate cancer patients.

Research methods

Between April 1998 and February 2011; 173 patients with intermediate and high risk disease were treated. Radiotherapy was delivered by either three-dimensional-conformal technique to a

total dose of 73.4 Gy at the ICRU reference point or intensity modulated radiotherapy technique to a total dose of 76 Gy. All the patients received 3 mo of neoadjuvant ADT followed by RT and additional 6 mo of ADT. ASTRO Phoenix definition was used to define biochemical relapse.

Research results

Median follow up duration was 125 months. Ninety-six patients (56%) had castrate testosterone level < 20 ng/dL and 139 patients (80%) had castrate testosterone level < 50 ng/dL. Both values are valid at predicting BRFS. However, patients with testosterone < 20 ng/dL have significantly better BRFS compared to other groups (P = 0.003). When we compare two values, it was found that using 20 ng/dL is better than 50 ng/dL in predicting the BRFS (AUC = 0.63 *vs* 0.58, respectively).

Research conclusions

In current study serum testosterone was measured using modern immunoassay method. With a median follow up time of 125 mo, our treatment outcomes are in consistent with the literature supporting the use of lower castrate testosterone level. It seems that lowering testosterone levels below 20 ng/dL should be achieved for better treatment results. This might be achieved either by using long term ADT, total androgen blockage or novel antiandrogen treatments. Compared to similar studies previously described our patient have a homogenous treatment protocol and follow up duration is longer. All of the patients were treated according to our institutional treatment protocol and all received the planned treatment. All the follow ups were carried out at a single center using the same lab. Thus, all patients seem to have more homogenous treatment and follow up.

Research perspectives

In this study we demonstrated that castrate testosterone level of less than 20 ng/dl achieved after primary RT plus ADT is associated with better BRFS. Using castrate cut off value of 20 ng/dL is better in estimating the BRFS compared to 50 ng/dL. Further studies using current standard of care of high dose IMRT and longer ADT duration might support these findings.

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CASE REPORT

Wilms tumor with dilated cardiomyopathy: A case report

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Author contributions: Sethasathien S and Silvilairat S identified the patient, designed the study, and wrote the manuscript; Choed-Amphai C, Sathitsamitphong L and Charoenkwan P wrote the manuscript; Choed-Amphai C, Saengsin K, Sathitsamitphong L, Charoenkwan P and Tepmalai K provided study materials; All authors read and approved the final manuscript.

Informed consent statement: The patient's parent gave written informed consent for the publication of this case.

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Abstract

BACKGROUND

Wilms tumor is the most common renal malignancy in childhood. It occurs primarily between the ages of 2 and 5 years. The usual manifestations are abdominal mass, hypertension, and hematuria. The case presented here had an unusual presentation, with dilated cardiomyopathy and hypertension secondary to the Wilms tumor.

CASE SUMMARY

A 3-year-old boy presented with a 5-d history of irritability, poor appetite, and respiratory distress. His presenting clinical symptoms were dyspnea, tachycardia, hypertension, and a palpable abdominal mass at the left upper quadrant. His troponin T and pro-B-type natriuretic peptide levels were elevated. Echocardiography demonstrated a dilated hypokinetic left ventricle with an ejection fraction of 29%, and a suspected left renal mass. Computed tomography scan revealed a left renal mass and multiple lung nodules. The definitive diagnosis of Wilms tumor was confirmed histologically. The patient was administered neoadjuvant chemotherapy and underwent radical nephrectomy. After surgery, radiotherapy was administered, and the adjuvant chemotherapy was continued. The blood pressure and left ventricular function normalized after the treatments.

CONCLUSION

Abdominal mass, dilated cardiomyopathy and hypertension can indicate Wilms tumor in pediatric patients. Chemotherapy and tumor removal achieve successful

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E-Editor: Qi LL

treatment.

Key words: Dilated cardiomyopathy; Heart failure; Hypertension; Wilms tumor; Case report

Core tip: Wilms tumor is the most common renal malignancy in childhood. The usual manifestations are abdominal mass, hypertension, and hematuria. A 3-year-old male presented with an unusual clinical profile of dilated cardiomyopathy and hypertension secondary to Wilms tumor. Echocardiography demonstrated a dilated left ventricle with poor contractility and a suspected left renal mass. The definitive diagnosis of Wilms tumor was confirmed histologically. Wilms tumor should be included in the differential diagnosis of any pediatric patient with dilated cardiomyopathy and abdominal mass, regardless of the presence of hypertension. Treatment of chemotherapy and tumor removal resulted in an improvement of left ventricular function.

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INTRODUCTION

Wilms tumor, also known as nephroblastoma, is the most common renal malignancy in childhood and the second most common intraabdominal malignancy, accounting for 6% of all pediatric tumors. The age-adjusted incidence rate of Wilms tumor in Thailand is 2.7 per million[1]. Wilms tumor occurs primarily between the ages of 2 and 5 years[2], and the typical presentation is an asymptomatic abdominal mass. Other signs and symptoms are abdominal pain, hematuria, and hypertension; although, dilated cardiomyopathy and congestive heart failure are additional yet unusual presentations in patients with Wilms tumor, with only five cases reported previously[3-6]. On the other hand, pheochromocytoma could also be suspected in a patient with acute myocarditis or dilated cardiomyopathy and hypertension[7-10]. Intracaval and intracardiac extension of the tumor thrombus is a cardiovascular complication occurring in 4%-10% of Wilms tumor[11-13]. This report describes a pediatric case of Wilms tumor with an unusual presentation of dilated cardiomyopathy with hypertension that was determined to be secondary to the tumor.

CASE PRESENTATION

Chief complaints

A 3-year-old boy presented with acute myocarditis and congestive heart failure.

History of present illness

The patient was hospitalized at a primary hospital, with a 5-d history of irritability, poor appetite, and respiratory distress. A chest radiograph revealed mild cardiomegaly and pulmonary infiltration. The patient was treated for bacterial pneumonia with a 3-d regimen of an oral antibiotic. He was then referred to a provincial hospital due to his symptoms not improving. His vital signs were as follows: heart rate of 144/min; respiratory rate of 65/min; blood pressure of 145/94 mmHg (right arm) and 144/102 mmHg (left arm), and of 169/90 mmHg (right leg) and 150/119 mmHg (left leg). He had dyspnea, tachycardia, hepatomegaly, and an oxygen saturation of 97%. Bilateral fine crepitations were audible over both lungs. Cardiac examination detected no murmur, regular rhythm, and normal first and second heart sounds, but also revealed an S_3 gallop. His liver was palpated 6 cm below the right costal margin.

A firm, non-tender mass was detected at the left upper quadrant of the abdomen,

with the lower border at 8 cm below the left costal margin, and was suspected to be an enlarged spleen. A chest radiograph showed mild cardiomegaly and diffuse pulmonary infiltration. Electrocardiography noted a condition of sinus tachycardia and left ventricular (LV) hypertrophy. The two-dimensional and color Doppler echocardiography demonstrated presence of a hypokinetic LV wall with an ejection fraction of 29%, no mitral regurgitation, and normal coronary anatomy. The patient was diagnosed with acute myocarditis and treated with intravenous immunoglobulin, milrinone, furosemide, and spironolactone. He was referred to the Chiang Mai University Hospital (Chiang Mai, Thailand) because of the acute myocarditis, poor LV contractility, and hypertension.

History of past illness

The patient was reportedly healthy before the present illness.

Physical examination

The patient had hypertension and a mass at the left upper quadrant of the abdomen, with the lower border at 8 cm below the left costal margin and suspected to be splenomegaly.

Laboratory testing

On admission, the blood chemistry exam revealed normal renal function, elevated liver enzymes (aspartate aminotransferase 119 U/L, normal: 0-40 U/L; alanine aminotransferase 139 U/L, normal: 0-41 U/L), slightly elevated troponin T (50 pg/mL, normal: ≤ 14 pg/mL), elevated CKMB (6.1 ng/mL, normal: < 4.8 ng/mL), and markedly elevated pro-B-type natriuretic peptide (21,736 pg/mL, normal: < 300 pg/mL). Urinary analysis showed microscopic hematuria. The patient also had substantially elevated serum chromogranin A (156.9 ng/mL, normal: 31-94 ng/mL), plasma renin activity (34.75 ng/mL/h, normal: 0.06-4.69 ng/mL/h), and plasma aldosterone (961 pg/mL, normal: 20-180 pg/mL). The urinary level of metanephrines was within normal range (56.15 μg/d, normal: 25-312 μg/d).

Imaging examination

A chest radiograph revealed cardiomegaly with a cardiothoracic ratio of 60% and diffuse small pulmonary nodules (Figure 1A). Echocardiography was performed to determine the cause of the acute myocarditis and hypertension. A dilated left ventricle with poor contractility (LV ejection fraction of 30%) and an 8 cm × 9 cm left renal mass were demonstrated (Figure 2). Chest and abdominal computed tomography (commonly referred to as CT) scans delineated the existence of a large lobulated heterogeneously hypoenhancing 9.7 cm × 9.7 cm × 9.5 cm soft tissue mass occupying the left kidney, with intralesional necrotic and non-enhancing cystic portions (Figure 3A). In addition, a thrombus in the left renal vein, ascites, multiple pulmonary nodules, and mediastinal lymphadenopathy were noted. Wilms tumor with lung metastasis was suspected.

FINAL DIAGNOSIS

A core needle biopsy of the mass was performed to confirm the diagnosis. The tissue histology revealed the triphasic pattern of Wilms tumor and absence of anaplasia.

TREATMENT

The patient received intravenous milrinone, furosemide, spironolactone, enalapril, amlodipine, and prazosin for treatment of the LV dysfunction with congestive heart failure and hypertension. Also, low molecular weight heparin was administered for treatment of his left renal vein thrombosis. Neoadjuvant chemotherapy (using a regimen of etoposide and carboplatin) was initiated.

OUTCOME AND FOLLOW-UP

Chest and abdominal CT scans after the first course of chemotherapy revealed a decrease in size of the tumor mass and newly developed pulmonary embolism in the left descending artery supplying basal segments of the left lower lobe. However, the patient showed no sign of deterioration. The planned radical nephrectomy was postponed because of the patient's very large tumor mass, ascites, and pulmonary

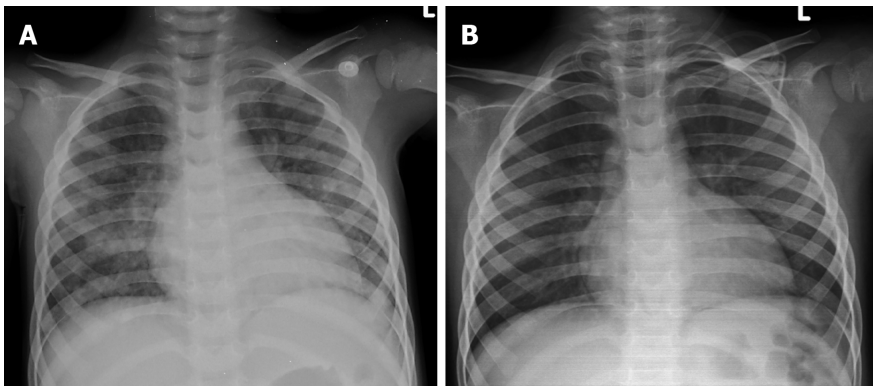

Figure 1 Chest radiographs. A: At initial presentation, cardiomegaly with a cardiothoracic ratio of 60% and diffuse small multiple pulmonary nodules was detected; B: After three courses of chemotherapy, cardiomegaly with a cardiothoracic ratio of 55% and absence of pulmonary nodules was detected.

embolism. After three courses of chemotherapy, the tumor mass decreased in size, measuring 5.7 cm × 5.1 cm × 5.8 cm in the axial and vertical diameters, respectively (Figure 3B). A chest radiograph revealed mild cardiomegaly with a cardiothoracic ratio of 55% and absence of pulmonary nodules (Figure 1B). A chest CT scan showed marked decrease in the size and number of pulmonary nodules.

At 3 mo after the initiation of treatment, the patient had no clinical evidence of congestive heart failure. Echocardiography demonstrated improved LV contractility, with an ejection fraction of 50%. An adjuvant chemotherapy comprising dactinomycin, vincristine and doxorubicin was administered. The left radical nephrectomy was then performed at 4 mo after the diagnosis (Figure 4). The postoperative histopathological report confirmed Wilms tumor with triphasic pattern and absence of anaplasia. After surgery, the patient underwent radiation therapy to the whole lung and left flank, while the adjuvant chemotherapy was continued. His plasma renin decreased to a normal level (2.83 ng/mL/h); blood pressure normalized and echocardiography showed good LV contractility, with an ejection fraction of 58%.

DISCUSSION

This present case had an unusual presentation of dilated cardiomyopathy and hypertension secondary to Wilms tumor. Dilated cardiomyopathy and congestive heart failure are rare presenting signs and symptoms of Wilms tumor, of which there have been only five reported cases previously[3-6]. All of the reported cases, along with our case presented herein, are summarized in Table 1. Hypertension accompanied by dilated cardiomyopathy was noted in three of the five previously reported patients with Wilms tumor. Also, three of the five previously reported cases showed hyperreninemia with hypertension and congestive heart failure. Trebo *et al*[5] reported two cases of Wilms tumor with dilated cardiomyopathy and absence of hyperreninemia. The authors postulated that vasoactive mediators other than renin being produced from the Wilms tumor as the cause of the dilated cardiomyopathy without hypertension or elevated renin. The removal of the Wilms tumor alleviated the deterioration of the cardiac function in both of those previous cases.

Systemic hypertension secondary to high serum renin is common. Two hypotheses have been proposed for the etiology of hyperreninemia, including a mechanical compression of the renal artery leading to renal ischemia and a production of renin by the Wilms tumor[14-16]. In our case, the tumor mass displaced the left renal vessels, with a gross invasion causing a filling defect of thrombus in the left renal vein that was likely the cause of the elevated serum renin. The hyperreninemia resulted in increased angiotensin II, aldosterone and vasoconstriction, as well as fluid retention, all leading to hypertension and dilated cardiomyopathy. In addition, several studies have demonstrated that angiotensin II plays an important role in cardiac remodeling and dysfunction, regardless of the hemodynamic abnormality[17-19]. After treatment with chemotherapy, the size of our patient's tumor mass decreased and the LV function gradually improved. In addition, his LV contractility returned to normal after the left radical nephrectomy.

Wilms tumor is characterized by a tendency to invade blood vessels. Extension of a tumor thrombus along the renal vein into the inferior vena cava and right atrium occurs in 4%-10% of all patients with Wilms tumor[11-13]. In the present case, the

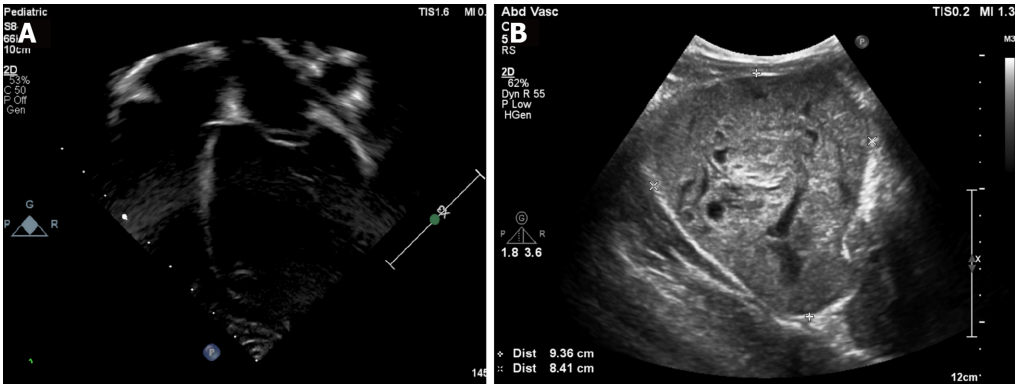

Figure 2 Echocardiography. A: A dilated left atrium and a left ventricle with poor contractility were noted; B: A 8 cm× 9 cm left renal mass with multilocular renal cyst appearance was seen.

thrombus was noted in the left renal vein and a pulmonary embolism developed in the left descending artery supplying basal segments of the left lower lobe. Furthermore, Wilms tumor can cause hematogenous metastasis to the lymph nodes, lung, liver, bone, or brain. The case presented herein represented Wilms tumor stage 4 with multiple pulmonary metastases and mediastinal lymphadenopathy.

CONCLUSION

An abdominal mass with or without hematuria and hypertension is a common presentation, whereas dilated cardiomyopathy is an uncommon presenting symptom in patients with Wilms tumor. Wilms tumor should be included in the differential diagnosis of any patient, particularly pediatric, with dilated cardiomyopathy and an abdominal mass, regardless of the presence of hypertension. In a patient with acute myocarditis or dilated cardiomyopathy with hypertension in which other causes of hypertension are not identified, an abdominal ultrasound should be performed.

Table 1 Clinical characteristics, laboratory findings, treatment and outcome in patients with Wilms tumor and dilated cardiomyopathy

Ref.	Age, sex	Primary tumor (size)	Stage	Presenting symptoms	Laboratory findings	Treatment and outcome
Stine *et al*[3], 1986	9 mo, male	Bilateral kidneys (11 cm× 11 cm × 9 cm, 13 cm × 13 cm × 9 cm)	V	Abdominal distension, CHF, HT	Hyperreninemia, increased aldosterone level	Chemotherapy, partial nephrectomy; Resolved CHF/HT after 3 mo
Agarwala *et al*[4], 1997	2 yr, female	Right kidney (10 cm × 15 cm × 8 cm)	II	CHF, pulmonary edema, DCM, HT	Hyperreninemia	Right nephrectomy, chemotherapy; Resolved CHF/HT after 1 yr
Trebo *et al*[5], 2003	2.5 yr, female	Right kidney	IV	DCM, no HT	Normal renin level	Right nephrectomy, chemotherapy, radiotherapy; Resolved CHF/HT after 3 yr
	8 mo, female	Right kidney	I	DCM, HT	Normal renin level	Right nephrectomy; Resolved CHF/HT after 2 mo
Chalavon *et al*[6], 2017	7 mo, female	Right kidney (8.5 cm × 10 cm × 8 cm)	I	CHF, pulmonary edema, DCM, no HT	Hyperreninemia, increased angiotensin II level	Right nephrectomy, chemotherapy; Resolved CHF/HT after 10 mo
Present case, 2018	3 yr, male	Left kidney (9.7 cm × 9.7 cm × 9.5 cm)	IV	CHF, DCM, HT	Hyperreninemia, increased aldosterone level	Left nephrectomy, chemotherapy, radiotherapy; Resolved CHF/HT after 3 mo

CHF: Congestive heart failure; DCM: Dilated cardiomyopathy; HT: Hypertension.

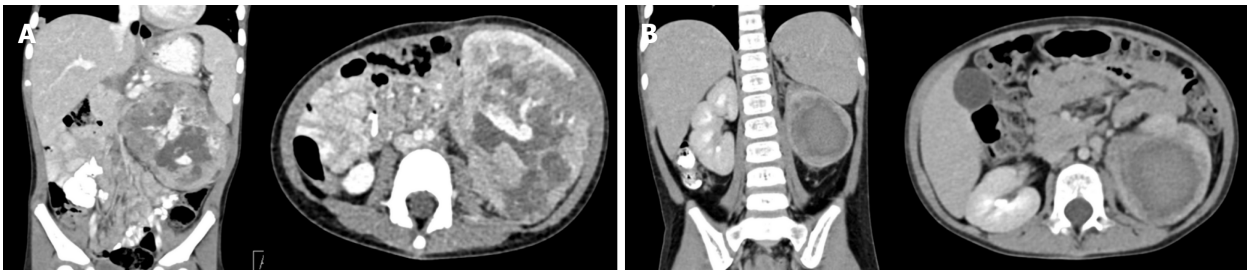

Figure 3 Computed tomography scan of the abdomen. A: At initial presentation, a large lobulated heterogeneously hypoenhancing 9.7 cm × 9.7 cm × 9.5 cm soft tissue mass occupying the left kidney was detected; B: After three courses of carboplatin and etoposide, the tumor was found to have decreased in size to measure 5.7 cm × 5.1 cm × 5.8 cm.

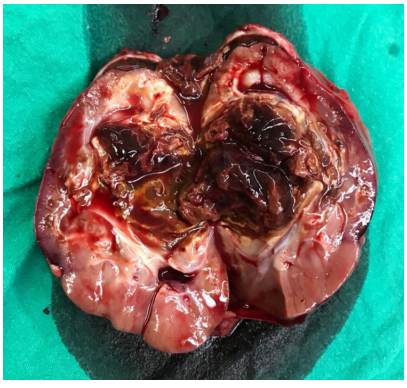

Figure 4 A Wilms tumor of 3.5 cm × 4 cm × 7.5 cm confined to the renal capsule with hemorrhagic necrosis of tumor cells was removed.

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