Symposium

# Monitoring of the upper urinary tract in patients with bladder cancer

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## ABSTRACT

Upper urinary tract (UUT) transitional cell carcinoma (TCC) is relatively rare tumor. Approximately 0.7-4% of patients with primary bladder cancer develops UUT-TCC. The symptoms related to an UUT-TCC often occur with an advanced stage which leads one to emphasize a surveillance strategy to monitor the UUT to allow for an earlier diagnosis. Although the risk of UUT-TCC after bladder cancer is well established, there is a paucity of recommendations suggesting the optimal method and frequency of monitoring the UUT and there is no consensus among them. This article reviews the recommendations on monitoring the UUT in patients with bladder cancer.

**Key words**: Bladder cancer, recurrence, transitional cell cancer, upper tract urothelial cancer

## INTRODUCTION

History of urothelial carcinoma (UC) in the bladder is a known risk factor for development of transitional cell carcinoma (TCC) in the upper urinary tract (UUT). The theory of multicentricity or pan-urothelial "field defect" suggests that the patients with UC in the bladder are at higher risk of developing UUT-TCC.[1,2] The incidence of UUT-TCC following UC of the bladder ranges from 0.7 to 4%.[1-10] Most of these tumors are diagnosed between 3 and 6 years after the initial diagnosis of bladder UC.[2,3,6,11] Several studies have shown that multicentricity, recurrent tumors, carcinoma in situ (CIS), vesicoureteral reflux (VUR) and Bacillus Calmette Guerin (BCG) treatment are the factors associated with greater risk of UUT-TCC after a diagnosis of bladder UC.[1,4,12-14] Recent reports have shown that risk stratification of the primary bladder cancer facilitates identifying patients with a higher risk of developing UUT-TCC.[3,4,15]

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The symptoms related to an UUT-TCC often occur only with an advanced stage which would lead one to emphasize a surveillance strategy to monitor the UUT to allow for an earlier diagnosis.[11] Although the risk of UUT-TCC after bladder cancer is well established, there is a paucity of recommendations suggesting the optimal method and frequency of monitoring the UUT and there is no consensus among them.[5] Most guidelines do not recommend routine monitoring of the upper tract for all patients with a history of UC of bladder; but favor imaging strategies based on risk stratification of the primary bladder tumor.

## EVIDENCE REVIEW

### *UUT-TCC after diagnosis of bladder cancer*

The proportion of patients developing metachronous UUT-TCC after a nonmuscle-invasive bladder cancer (NMIBC) varies from 0.7 to 4%.[5] However, if one selects only the high-risk NMIBC patients who received intravesical BCG, the incidence rate of subsequent UUT-TCC increases to 20-25%.[1,6,8,10,13,14] Table 1 lists published studies that focus on monitoring the UUT of bladder cancer patients.

Several authors have analyzed the biological behavior and etiological mechanism of UUT-TCC in patients in various risk groups. Yousem *et al.* followed 597 patients with UC of the bladder and reported that 3.9% (23) developed an UUT-TCC after an average interval of 61 months. They concluded that follow-up radiological examination of the UUT 1 year after the primary bladder UC would have allowed detection of 17% of the UUT-UC. A 2-year radiological exam would have enabled detection of 44%, for

**Table 1: UUT-TCC after NMIBC**

| Study | Year | No. of patients | UUT-TCC % | Follow-up | Cohort characteristics |
|---|---|---|---|---|---|
| Skinner *et al*.[47] | 1974 | 59 | 5.1 | 27 | BC |
| Walzer *et al*.[48] | 1983 | 337 | 0 | 96 | BC |
| Amar *et al*.[12] | 1985 | 269 | 0.44<br>6.44 | 36 | BC (No VUR)<br>BC (VUR) |
| Yousem *et al*.[16] | 1988 | 597 | 3.9 | 60 | BC |
| Oldbring *et al*.[11] | 1989 | 657 | 1.7 | 120 | BC |
| Schwartz *et al*.[8] | 1992 | 638 | 3.1 | | BC |
| Holmang *et al*.[17] | 1998 | 680 | 2.4 | 60 | BC |
| Solsona *et al*.[10] | 1997 | 786 | 2.3 | | BC |
| Solsona *et al*.[10] | 1997 | 138 | 24.6 | | CIS |
| Canales *et al*.[3] | 2006 | 3375 | 3.4 | 72 | Ta tumors |
| De Torres *et al*.[13] | 1987 | 288 | 0.9<br>20 | | NMIBC (No VUR)<br>NMIBC (VUR) |
| Shinka *et al*.[18] | 1988 | 519 | 2.3<br>13.2 | | NMIBC<br>NMIBC (Occu.BC) |
| England *et al*.[49] | 1981 | 332 | 1.5 | 60 | High-risk (T1) |
| Miller *et al*.[14] | 1993 | 82 | 13.4 | 62 | High-risk BCG |
| Herr *et al*.[1] | 1996 | 86 | 21 | 180 | High-risk BCG |
| Herr *et al*.[15] | 1998 | 307 | 25 | 144 | High-risk BCG |
| Hurle *et al*.[4] | 1999 | 216<br>182<br>193 | 0.9<br>2.2<br>9.8 | 60 | Low risk<br>Intermediate risk<br>High risk |
| Millan Rodriguez *et al*.[2] | 2000 | 1529 | 0.6<br>1.8<br>4.1 | | Low risk<br>Intermediate risk<br>High risk |

UUT-TCC, Upper urinary tract-transitional cell carcinoma; NMBIC, Nonmuscle-invasive bladder cancer; BC, Bladder cancer; VUR, Vesicoureteral reflux.

**Table 2: Definitions evidence levels**

| | |
|---|---|
| Level 1 | Meta-analysis of RCTs or good quality RCT |
| Level 2 | Low-quality RCT or meta-analyses or good quality prospective cohort studies |
| Level 3 | Good quality retrospective case-control studies and case studies |
| Level 4 | Expert opinion based on "first principles" or bench research, not on evidence |

RCT, Randomized control studies.

a total of 61%. This report recommends annual intravenous or retrograde pyelography following diagnosis for the first 2 years, followed by biennial examinations unless clinical or cytological evidence warrants earlier evaluation.[16]

Oldbring *et al*.[11] reported an incidence of metachronous UUT-TCC in 1.7% of 657 patients with primary bladder UC followed for 10 years. Of the 11 patients with UUT-TCC, three were diagnosed on excretory urography and five were only found at autopsy. The authors also noted that the initial or recurrent bladder UC involved the ipsilateral ureteral orifice in six patients. They concluded that routine radiological examination is not indicated in the absence of symptoms and it should be reserved for patients with multiple and recurrent bladder tumors or tumors involving the ureteral orifice.[11] Similarly, Holmang *et al*.[17] reported a 2.4% incidence of UUT-TCC in 680 patients with primary bladder UC and recommended urography at (1) initial diagnosis of bladder UC, (2) when bladder tumor progression occurs or (3) when symptoms and signs suggest UUT disease.

Solsona *et al*. suggest that patients with bladder CIS have a higher risk of developing UUT-TCC. In their analysis, 138 patients with bladder CIS and 786 with NMIBC without CIS were studied and 24.6% and 2.3%, respectively, developed UUT-TCC. The UUT-TCC incidence was significantly higher in patients with bladder CIS than in patients with any NMIBC or patients with muscle-invasive bladder cancer (MIBC) treated by cystectomy (3.9%). Moreover, 32% of patients with bladder CIS who developed UUT-TCC had bilateral UUT-TCC and 67% had prostatic involvement by UC.[10]

Amar *et al*. and De Torres *et al*.[12,13] reported that the main factor in the development of a metachronous UUT-TCC is VUR. Patients with bladder UC and VUR have several fold greater risk of developing UUT-TCC. Since one in five patients with VUR after transurethral resection may develop UUT-TCC, these authors recommended closer follow-up.[13] In addition, Shinka *et al*.[18] reported a higher incidence (13%) of UUT-TCC in dye workers with bladder UC compared with the general population with bladder UC.

Miller *et al*. and Herr *et al*. evaluated the long-term incidence of upper tract tumors in patients with high-

**Table 3: Risk stratification of bladder cancer**

| Risk | AUA | EAU | NCCN |
|---|---|---|---|
| Low | Low-grade Ta<br>Small volume | G1-G2 Ta | G1-G2 Ta |
| Intermediate | Low-grade multifocal/ Large volume Ta | Multifocal G2Ta<br>G1T1, Solitary G2T1 | G3Ta<br>Solitary G1-2 T1 |
| High | High-grade Ta<br>Any T1<br>CIS | Any high grade<br>Multifocal G2T1<br>CIS | G3T1<br>Multifocal T1 |

AUA, American Urological Association; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network

**Table 4: Studies reported UUT-TCC after RC for MIBC**

| Study | Year | No. of patients | No. of UUT-TCC | UUT- TCC (%) | Detected by presenting symptom | Median time (months) | Risk factors |
|---|---|---|---|---|---|---|---|
| Zincke *et al*.[39] | 1984 | 425 | 14 | 3.3 | | 40 | Ureteral involvement, multifocal TCC, CIS |
| Hastie *et al*.[30] | 1991 | 180 | 10 | 1.8 | | | |
| Tsuji *et al*.[50] | 1996 | 61 | 5 | 8.2 | | 69* | |
| Kenworthy *et al*.[32] | 1996 | 430 | 11 | 2.6 | 45 | 40 | Ureteral involvement |
| Solsona *et al*.[10] | 1997 | 215 | 16 | 7.4 | | 58 | Multifocal TCC, Prostatic urethral involvement, organ-confined TCC |
| Slaton *et al*.[23] | 1999 | 382 | 9 | 2.4 | 44 | 25 | |
| Balaji *et al*.[28] | 1999 | 529 | 16 | 3.0 | 56 | 37 | Ureteral involvement |
| Huguet-Perez *et al*.[31] | 2001 | 568 | 26 | 4.5 | 58 | 46* | NMIBC, VUR |
| Yossepowitch *et al*.[38] | 2003 | 483 | 10 | 2.1 | | | |
| Sved *et al*.[35] | 2004 | 235 | 5 | 2.0 | 80 | 40* | Prostatic urethral involvement |
| Akkad *et al*.[27] | 2006 | 84 | 2 | 2.3 | 100 | 62* | Recurrent TCC, multifocal TCC |
| Sanderson *et al*.[34] | 2007 | 1069 | 27 | 2.5 | 78 | 40 | Urethral involvement |
| Furukawa *et al*.[29] | 2007 | 583 | 12 | 2.1 | | 30 | Multifocal<br>Recurrent TCC |
| Meissner *et al*.[33] | 2007 | 322 | 15 | 4.7 | 47 | 36 | Positive ureteral margins |
| Tran *et al*.[36] | 2008 | 1329 | 80 | 6.0 | | 25 | Ureteral involvement |
| Volkmer *et al*.[37] | 2009 | 1420 | 25 | 1.8 | 52 | 39 | Ureteral involvement, NMIBC, recurrent TCC, CIS |
| | | 8254 | 278 | 3.4 | 62 | 40 | |

*Mean. UUT-TCC, Upper urinary tract-transitional cell carcinoma; NMBIC, Nonmuscle-invasive bladder cancer; BC, Bladder cancer; CIS, Carcinoma *in situ*; VUR, Vesicoureteral reflux; MIBC, Muscle-invasive bladder cancer; RC, Radical cystectomy

**Table 5: EAU recommendation on follow-up for MIBC after RC[44]**

| Stage at RC/ Study | 3 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|---|---|---|
| pT1 | | | | | | | | | |
| CT/MRI | X | X | X | | X | | X | X | X |
| Cytology | | | X | | X | | X | X | X |
| pT2 | | | | | | | | | |
| CT/MRI | X | X | X | X | X | | X | X | X |
| Cytology | | X | X | | X | | X | X | X |
| >pT3/N+ | | | | | | | | | |
| CT/MRI | X | X | X | X | X | X | X | X | X |
| Cytology | X | X | X | | X | X | X | X | X |

MIBC, Muscle-invasive bladder cancer; RC, Radical cystectomy

risk NMIBC who were treated with BCG. All patients underwent upper tract studies within 3 months of starting BCG treatment. After following 82 consecutive patients for a median follow-up of 62 months, Miller *et al.* reported 11 patients (13.4%) with metachronous UUT-TCC. The median interval between BCG therapy and diagnosis of UUT-TCC was 38 months with a range of 7-110. Eight of the 11 patients were diagnosed by abnormal surveillance intravenous or retrograde pyelogram and seven had positive cytology. Positive cytology alone directed the

diagnosis in two patients. One patient was diagnosed after the work-up for hematuria.[14]

Hurle *et al*. stratified 591 bladder UC patients into low, intermediate and high risk for UUT-TCC. Patients with low grade (G1-2) and stage (Ta-1) solitary tumors were grouped as low risk and patients with high grade (G3) NMIBC, CIS or failure to respond to intravesical chemotherapy were considered high risk. After a median follow-up of 86 months, 0.9% of low, 2.2% of intermediate and 9.8% of high-risk patients developed UUT-TCC. There was a statistically significant greater risk of UUT in patients with high-risk bladder UC when compared with those with low and intermediate risk. They recommended annual intravenous pyelogram and urine cytology every 4 months for high-risk NMIBC patients.[4] Milan-Rodriguez *et al*.[2] studied the UUT-TCC evolution in a cohort of 1529 patients and concluded that a higher risk of UUT must be expected in cases of multicentric NMIBC (relative risk 2.7, CI 1.06-6.84).

Several studies have confirmed that high-risk bladder UC patients have a greater risk of developing UUT-TCC (Evidence Level 3; Table 2) and recommend regular surveillance. However, the risk of UUT-TCC and the optimal surveillance guidelines for stage Ta tumors continues to be controversial. Canales *et al*. followed 375 patients with stage Ta bladder UC. They found 3.4% UUT-TCC with an average duration of 22 months after the initial diagnosis of bladder UC. The median follow-up was 6 years. In their analyses, stage Ta bladder UC patients with two or more recurrences within a median of 12 months or less are at a higher risk (Relative risk 4.5) for developing UUT and should be considered for surveillance.[3]

Transurethral resection of bladder tumors is the gold standard for initial diagnosis and treatment of Ta, T1 and CIS.[19] Depending on the morphology and pathology of the primary bladder tumor, these patients undergo risk stratification. The guidelines of the American Urological Association (AUA), European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN), all stress the importance of risk groups.[19-21] There are minor differences among the risk groups and the follow-up recommendations. Table 3 illustrates the bladder cancer risk stratification. Tumors with a small chance to recur or progress are grouped as low risk and tumors with a high likelihood of recurrence and progression are grouped as high risk. The intermediate tumors have a high chance to recur and low chance to progress.

The guidelines recommend UUT surveillance in bladder UC patients based upon the risk groups. AUA guidelines recommend "periodic" upper tract imaging, especially for high-risk patients.[19] They also warn that UUT-TCC may occur in a higher proportion of patients with CIS in the bladder. However, it does not specify the frequency of imaging or a specific surveillance protocol. There was no specific recommendation given for low and intermediate risk groups.[19]

The EAU states that patients with high-risk bladder UC should undergo annual upper tract imaging and low-risk patients do not benefit from UUT surveillance. Those in the intermediate group should be risk adapted according to the individual patient factors.[20] (Evidence level 2 and 3) EAU guidelines recommend intravenous urography or CT urography in patients where the primary bladder tumor was located in the trigone. They predict a higher incidence (7.5%) of synchronous UUT-TCC in these patients.

NCCN recommends an imaging study of the UUT every 1-2 years for intermediate and high-risk patients. They mention that urinary urothelial tumor marker assessment is optional in these patients. Low-risk patients do not need any UUT studies.[21] (Evidence level 2) The First International Consultation on Bladder Tumors recommended lifelong follow-up for CIS patients even there is a complete response to intravesical therapy, due to high risk of recurrence and progression.[22]

### *Summary of evidence*

The incidence of UUT-TCC in primary bladder cancer patients is strongly related to the primary tumor risk stratification. The incidence is as low as 0.7% in the low-risk group followed a median of 10 years to as high as 24% in high-risk groups followed 3-4 years.[5] High grade (G3), bladder CIS (Tis), stage T1, multiple and recurrent tumors of any stage are risk factors for UUT-TCC. The symptoms of UUT-TCC may present at an advance stage with a higher mortality.[5,20] High-risk patients should probably undergo upper tract imaging annually for the first 5 years and then every 2 years. Intermediate risk patients should be offered UUT imaging based on individual patient factors. Low-risk patients may be offered imaging of UUT upon symptoms or stage or grade progression. The imaging study can be either retrograde or intravenous urography or CT urography. Most of the preferred imaging modalities require intravenous contrast which infrequently may result in significant morbidity. In addition, all these patients have radiation exposure during these imaging studies. Clinicians should make sure that the benefits of a surveillance test should over weigh the cumulative risk. Urinary cytology and other urine-based markers are optional (Evidence level 2).

### *UUT-TCC after radical cystectomy*

Radical cystectomy (RC) is the standard of care for MIBC. Eighty percent of those that recur do so within 2-3 years. The majority of early recurrences are detected successfully through routine surveillance.[23] On the contrary, late recurrences are commonly detected in the UUT. Despite

routine surveillance, late UUT recurrences are detected only after developing tumor-related symptoms.[24] Although the prognosis is generally poor, long-term survival can be achieved in a subset of patients after radical nephroureterectomy.[25]

The overall risk of UUT-TCC following RC for bladder UC ranges from 2 to 7% with most tumors within 2-4 years of surgery.[26] We identified 15 reports including nine large series with a sample size over 400. Together the 15 reports analyzed a total of 8254 patients who underwent RC.[10,23,27-39] Of these, 278 patients (3.4%) developed UUT-TCC over an average interval of 40 months between RC and UUT-TCC. Table 4 lists the individual studies published in the last two decades. Wright *et al*.[40] reported a 3.1% incidence of UUT-TCC following RC in a large population-based data (n=6216). The majority of the contemporary series reported a median interval of 30-40 months between RC and UUT-TCC diagnosis, with the exception of two studies where the interval was 25 months.[28,34,36] These two studies may have missed synchronous tumors detected after RC or had shorter follow-up. Tran *et al*. studied 1329 post RC patients and reported a 4% incidence at 3 years and 7% at 5 years. They also showed that the 3-year-risk of UUT-TCC remains 4-6% at any point measured up to 4 years after RC. This finding strongly supports continued vigilance for UUT relapse following RC.[36]

Almost every individual report attempted to identify the risk factors for UUT-TCC. Patients with good prognostic factors at RC are at higher risk of developing UUT-TCC.[24,37] Patients with organ confined disease obviously have a longer survival and are more prone for late relapse. Balaji *et al.* reported that more than two-thirds of UUT-TCC occur in patients with organ-confined disease.[28] Ureteral involvement of the bladder tumor was identified as a risk factor for ipsilateral UUT relapse. Volkmer *et al*.[37] reported a relative risk of 2.7 if there was tumor involvement in the distal intramural ureter. Following the analysis of 1069 patients Sanderson *et al.* reported that urethral involvement is the only factor associated with UUT-TCC. Although CIS is a well-known risk factor for UUT-TCC in NMIBC, its role in invasive bladder cancer is not certain.[34] Solsona *et al*.[10] reported significantly higher rates of UUT-TCC in patients undergoing RC for CIS. However, other larger series did not support this finding. It is unclear whether a positive ureteric margin at frozen section during the RC or as seen in the final pathology is a risk factor for a subsequent UUT-TCC. There is some evidence that TCC at the ureteric margin is associated with a higher risk of UUT-TCC, but it does not influence survival.[41] Moreover, achieving negative ureteral margins at RC does not eliminate the risk of subsequent UUT-TCC.[25] Other proposed risk factors are prostatic urethral involvement and multifocal and recurrent UC. From the published data more than 80% of all patients with UUT-TCC had at least one risk factor.[37]

Despite use of regular imaging, UUT-TCC is mainly diagnosed by symptoms-initiated examination. An average of 62% of UUT-TCC were detected by symptoms such as gross hematuria, flank pain, pyelonephritis or weight loss. Most of these tumors are advanced at the time of presentation and have a poor survival.[26] Routine surveillance of UUT does not appear to improve the survival in many series. Seventy to eighty percent will still die of UUT-TCC.[25]

Currently, UUT surveillance is primarily done by urine cytology and imaging; however, optimal duration, mode and interval of testing have not been established. Urine cytology is the most simple screening test for UUT-TCC.[42] Although the specificity of cytology is 95%, its overall sensitivity is as low as 60%.[43] Cytology was the primary mode of detection in less than 27% of UUT-TCC after RC when routinely used in the surveillance.[28,31,35] Sensitivity of urine cytology is highly dependent on tumor stage and grade as well as the experience of the cytopathologist. Several new molecular-based urine tests such as nuclear matrix protein-22 and fluorescence in situ hybridization are increasingly used in surveillance; however, the efficacy and accuracy of these methods for patients with a urinary diversion remains unclear.[42]

Imaging studies such as intravenous pyelogram or CT urography are the primary tools used in surveillance. The reported detection rate was less than 55% with IVP or CT urography.[23,27,28,31,32,35] CT detects 78-94% of lesions in the renal pelvis and only 19-53% are tumors within the ureter.[25] Tumors less than 2 cms are less likely to be detected by CT. Ultrasound and loopograms have a minimal role in detecting UUT-TCC. MR urography has not shown any advantage over CT except for patients with contrast allergies or in patients with compromised renal function who cannot receive intravenous contrast. Abnormalities in any of the above tests should prompt a retrograde pyelography and ureteroscopic evaluation with ureteral washings and biopsy of suspicious areas. Ureteroscopy in patients with urinary diversion is not easy as it may be challenging to identify the site of ureteral implantation to the reservoir and therefore, may necessitate an antegrade approach.

Several individual reports have raised the question whether all patients need to be monitored routinely for UUT-TCC given the small percentage of patients affected. Balaji *et al*.[28] concluded no routine radiological investigation was necessary for UUT in post-RC patients and recommended IVU for symptomatic patients. Other authors recommend an annual IVU or CT with urine cytology for the first 5 years.[24,31] Sved *et al*.[35] suggested biannual urine cytology and reserved IVU for symptomatic patients or patients with positive cytology. Few reports recommend "close surveillance" for patients with high risk of developing UUT-TCC. Kenworthy *et al*. categorized distal ureteric or prostatic involvement of TCC as a high-risk group and recommended

annual IVU and biannual urine cytology. All other patients are considered low risk and were recommended to have annual urine cytology and biannual IVU.[32] Similarly Slaton *et al*.[23] recommended annual IVU and urine cytology for organ-confined disease at RC. Patients with extravesical or node positive disease were recommended to have a CT at 6 months and then an annual CT and cytology.

### *Review of guidelines*

EAU guideline states that UUT surveillance regimens often fail to detect tumors before symptoms develop and recommend specific UUT imaging in case of clinical symptoms. However, the EAU guideline mandates follow-up oncological surveillance in all RC patients for 5 years with continued functional surveillance depending on the type of urinary diversion thereafter. The EAU recommendation includes UUT as shown in Table 5.[44] (Evidence level-4)

The recent NCCN practice guideline recommends close oncological surveillance for at least 2 years. Their protocol suggests urine cytology every 3-6 months and imaging of the chest, abdomen and pelvis including the upper tracts every 3-12 months for 2 years for patients after cystectomy. They recommend these as clinically indicated after 2 years.[21] (Evidence Level-3)

### *Summary of evidence*

UUT-TCC after RC for MIBC typically occurs after 2 years from surgery. Despite surveillance the majority of patients are diagnosed only at the onset of symptoms. Patients with tumor involvement of the intravesical portion of the ureter or urethra and a pathological RC stage of <pT2 are at higher risk of developing UUT-TCC.[34,45] CT and IVP are the standard imaging tests for surveillance. However, routine upper tract imaging does not appear to improve detection or survival. Despite its low sensitivity, urine cytology is a safe and relatively inexpensive test for high-grade TCC.[35] EAU guidelines recommend close oncological follow-up for at least 5 years and the NCCN for 2 years including an upper tract evaluation.[46] Although there is no consensus on a surveillance protocol, many individual reports recommend regular imaging of the UUT and urine cytology for high-risk groups. However, life-threatening high-grade tumors in the UUT are very unlikely to be detected "in time" by routine annual imaging. Urine cytology may be a beneficial and inexpensive surveillance tool. (Evidence level 4) Although UUT-TCC after radical cystectomy is rare, early detection and radical surgical treatment may prolong survival.

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