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Original Article

Colorectal Origin: A Marker of Favorable Outcome in Krukenberg Tumor? Results from Clinical and Prognostic Analysis

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Abstract

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This study aimed to identify the prognostic factors affecting the survival of patients suffering from Krukenberg tumor (KT) and also to determine the survival in these patients. A retrospective review of patients diagnosed with KT between January 2015 and December 2021 was conducted at a tertiary cancer center. Clinicopathological variables were scrutinized, and survival analysis was performed. Thirty-six patients were enrolled in this study. The median age at diagnosis was 48 years (ranging from 22 to 71 years). The median overall survival (OS) was 9.9 months (95% confidence interval [CI]: 6.6 to 13 months). The mean OS for tumors originating in the colorectal region was longer compared to that for tumors of other sites (15.4 vs. 9 months, respectively; $p = 0.048$). In univariate analysis, patients who received chemotherapy had better survival, while those presenting with ascites had a poor prognosis. No correlation was observed between age, menstrual status, bilaterality, size of ovarian metastases, extent of metastatic disease, metastasectomy, and survival. Multivariate Cox regression analysis showed that chemotherapy predicted a favorable survival outcome (hazard ratio [HR] = 0.200, 95% CI: 0.046–0.877, p-value = 0.033). KT is an aggressive tumor with a median OS of less than a year. Chemotherapy may improve survival. Patients with a primary tumor in the colorectal region have a better outcome, while those presenting with ascites indicate a poor prognosis.

Keywords

- Krukenberg tumor
- prognostic factors
- survival
- chemotherapy

Introduction

It has been more than a century since the Krukenberg tumors (KT) were first described, but the prognosis of this entity remains dismal. The World Health Organization defines KT as ovarian carcinoma characterized by the presence of stromal involvement, mucin-producing neoplastic signet-ring cells, and ovarian stromal sarcomatoid proliferation.[1]

KT is a rare tumor representing 1 to 2% of all ovarian malignancies.[2] The stomach, colorectal cancer (CRC), and

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breast are the most common primary sites of origin of KT[3]. The reason for predilection of these sites for metastasis to the ovaries is still obscure. The incidence of gastric cancer in females influences that of KT and as a result, the incidence of this disease is higher in Japan as compared to other parts of the world. The proportional incidence of the primary site, thus, depends on the local pattern of malignancies.

This tumor is diagnosed at a comparatively younger age, with an average age of 45 years in a premenopausal female.[4] The fact that gastric carcinomas are more commonly signet-ring cell type compared to other sites may be a cause, as signet-ring cell carcinoma has a younger age at presentation. Signet-ring cell carcinomas are associated with ovarian metastasis more often than other carcinomas with a ratio of about 4:1.[2]

Presence of KT is, in fact a poor prognostic factor itself, due to its tendency for extensive malignant spread within the abdominal cavity.[5] KT is considered an advanced stage disease bearing poor outcome due to its aggressive nature. The rarity of this entity has hindered the formation of definitive treatment protocols.

The main treatment modalities of these tumors include surgery and chemotherapy; however, the standard treatment and its sequence have not been established to date.[5] Ovaries act as a sanctuary site for cancer cells; therefore, chemotherapeutic drugs that have a good response in the primary site of origin generally have low response rates in the ovaries. Surgical intervention in the form of ovarian metastasectomy thus becomes an important alternative in the management of this malignancy.

The aim of this study was to document the presentation of patients reporting at our institute with KT, identify the prognostic factors affecting the survival of these patients, and determine the survival in our set of patients.

Materials and Methods

The records of our institution, a tertiary care center catering to the hilly Northern Indian state of Himachal, were reviewed, and patients who were diagnosed with KT between January 2015 and December 2021 were retrospectively identified.

Patients who were diagnosed with primary ovarian tumors were excluded from this study. Clinical information, imaging, tumor markers, endoscopy, and biopsy were used to rule out primary ovarian tumors. Additionally, multidisciplinary expert opinion was taken to correlate findings.

After scanning the patients' files, clinical and pathological variables were recorded. The determinants noted were age, menopause, pathological size of metastatic tumor (ovary), initial site of primary, disease extension, sequence, ascites, treatments, and procedures undertaken.

Overall survival (OS) was calculated from the date of diagnosis of the primary tumor or ovarian metastasis to the date of death or last follow-up. Metachronous disease was said to be present if the duration between the identification of disease and metastasis exceeded 6 months. SPSS software, version 23.0 (SPSS Inc., Chicago, Illinois, United States) was used for statistical analysis with two-sided p-value less than 0.05 being considered statistically significant. The data were represented as mean ± standard deviation and median (interquartile range) for normal and skewed distribution. Survival was calculated by Kaplan–Meier method. Univariate analysis using the log rank test was conducted for studying association of variables with OS. The calculation of prognostic importance of various variables as an expression of survival was performed by multivariate analysis utilizing the Cox proportional hazards regression model. The estimates were then shown as hazard ratio (HR) with 95% confidence interval (CI).

Results

Patient characteristics: Thirty-six patients were registered in our study. Baseline individual characteristics are listed in ►Table 1. The patients had a median age of 48 years, ranging from 22 to 71. Colorectal was the most common primary in 11 patients. Stomach primary was the second most common with seven patients. Other primary sites

Table 1 Baseline patient characteristics ($n = 36$)

	Characteristics	No. of Patients (%)
Age (years):	Median (range)	48(22-71)
Menopausal status	Premenopausal	19(53)
	Postmenopausal	17(47)
Primary site	Stomach	7(19)
	Colon and rectum	11(31)
	Gallbladder	5(14)
	Pancreas	3(8)
	Vermiform appendix	2(6)
	Unknown	8(22)
Ovarian involvement	Bilateral	27(75)
	Unilateral	9(25)
Tumor diameter (cm)	Median (range)	7.3(3-25)
	≤5	9(25)
	5-10	12(33)
	≥10	10(28)
	Not available	5(14)
Chronology	Synchronous	24(67)
	Metachronous	12(33)
Extent of disease	Ovary	10(28)
	Pelvis	3(8)
	Beyond pelvis	23(64)
Chemotherapy	Yes	22(61)
	No	14(39)
Ascites	Yes	21(58)
	No	15(42)
Metastasectomy	Yes	20(56)
	No	16(44)

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included the gall bladder, pancreas, and appendix. The primary site remained unknown in eight patients. Premenopausal and menopausal patients constituted almost equal proportions, with approximately 19 and 17, respectively. Ovarian metastasis that was metachronous was seen in 12 out of the 36 patients. It was a mixed population of patients, 8 patients had purely ovarian metastases, and 28 had diffuse metastases along with ovarian involvement.

Metastasectomy and chemotherapy were the treatment options utilized. Twenty patients had undergone metastasectomy. No surgical treatment was given to 16 patients, either due to additional metastatic lesions or advanced disease. Patients who exhibited a satisfactory response to treatment at the original location (>50% response rate) underwent a metastasectomy. The surgical procedures that were utilized included unilateral/bilateral adnexectomy or hysterectomy with bilateral adnexectomy.

Twenty-three patients received chemotherapy with the main drugs being docetaxel, cisplatin, carboplatin, oxaliplatin, and 5-fluorouracil. The patients who had colorectal primary received FOLFOX regimen +/− inj. Bevacizumab according to their affordability and feasibility. For stomach primaries, CAPOX chemotherapy was followed, while gall bladder and pancreatic cancers were treated with gemcitabine and cisplatin/CAPOX regimen. Patients who only had ovarian metastases received paclitaxel and carboplatin chemotherapy.

These were given as four to six cycles of two to three drug combinations. Both ovaries were involved in most cases i.e., 27. About one fourth of patients (28%) had big tumors (> 10 cm) with the median ovarian tumor size being 7.3 cm. Ten patients had ovarian metastasis only while the rest were having widespread metastasis to other organs like lung, bones, pelvis etc. Twenty-one patients had presented with ascites initially at diagnosis. Two patients with CRC each received bevacizumab and cetuximab as part of their targeted therapy. In these two cases, further RAS testing was carried out. Among these two, one patient was being treated with cetuximab for transverse colon cancer, and the other was being treated with bevacizumab for sigmoid colon primary.

Prognosis

On analysis of survival, it was observed that OS ranged from 0.5 to 54 months in the 36 patients with a median OS of 9.9 months (95% CI: 6.6–13 months) (►Fig. 1). Upon comparison of the different primary sites, we found that the OS of colorectal primaries is longer in contrast to primaries involving other sites (15.4 vs. 9 months respectively; $P = 0.048$). When comparing the primary site of stomach to other sites the difference in survival was not statistically significant. However, the presence of ascites at presentation was associated with a poorer prognosis (11.9 vs 16 months) compared to patients who did not have ascites initially ($p = 0.019$). Additionally, patients who received chemotherapy for treatment had a significantly better survival rate than the patients who did not receive it for any reason. (17.2 months vs. 8 months respectively; p value =0.001).

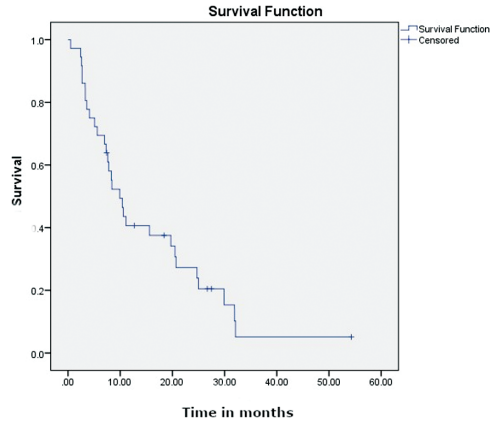

Fig. 1 Overall survival (OS) curve for all 36 patients. The median OS was 9.9 months (range, 0.5 -54 months).

Age of onset, bilateral tumors, size of ovarian metastases, menopause, extent of metastatic disease and metastasectomy were factors having no bearing on survival. Univariate analysis was done for these parameters, this also did not show any relationship with OS of patients, ($p > 0.05$) (►Table 2).

Chemotherapy also proved to be a significant factor in improving the OS on multivariate Cox regression analysis (HR = 0.200, 95% CI: 0.046–0.877, p value = 0.033) as compared to those who did not receive this treatment. No significant correlation was observed with any of the other parameters for predicting OS.

Discussion

Pathologists, radiologists, and physicians frequently work together to provide a conclusive diagnosis of KT. In our institution, the patients were diagnosed with KT based on the patient's clinical history, symptoms, and physical examination findings which were correlated with the primary tumor's origin. Imaging studies, endoscopy, and biopsies of the primary site had been performed to determine the origin of the metastasis. Immunohistochemistry (IHC) was used where feasible to analyze the tumor cells and determine their origin. Specific markers for various types of adenocarcinomas can help differentiate between primary ovarian tumors and metastatic tumors. IHC markers like CK7, CK20, CK 19, CDX2, PAX 8, CEA, GATB2, GATA 3, TTF1 were used in our patients to characterize tumors if needed (►Fig. 2) Imaging techniques such as ultrasound, computed tomography (CT) scans, and magnetic resonance imaging scans were used to identify the extent of ovarian involvement, any associated ascites (fluid accumulation), and potential primary sources of the tumor (►Fig. 3).

The advanced disease status associated with KT leads to poor outcomes and patients are only partially benefited by the various treatment options utilized in this disease. The treatment results in our subset of 36 patients also reflect the same.

The median age of diagnosis in our study population is 48 years. A similar age profile is seen in other series reported in the literature.[5,6] More than half of the patients were

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Table 2 Prognostic factors for Krukenberg tumor

FACTORS	*UNIVARIATE ANALYSIS*		*MULTIVARIATE ANALYSIS*	
	HR (95% CI)	*P* - value	HR (95% CI)	*P* - value
Age (>50 vs <50)	1.07 (0.03–1)	0.846		
Menstrual status (pre vs post menopausal)	1.13 (0.11 -1)	0.733		
Primary site (CRC vs others)	0.446 (0.197-0.997)	**0.048**	0.710 (0.229-2.204)	0.352
Primary site (stomach vs others)	1.619 (0.710-3.692)	0.247		
Ovarian involvement (u/l vs b/l)	0.770(0.313-1.894)	0.569		
Tumour diameter (>10 cm vs <10 cm)	0.799(0.372-1.714)	0.565		
Metachronous vs synchronous	1.326(0.624-2.820)	0.463		
Disease extent (Ovaries vs beyond pelvis)	0.441(0.178-1.090)	0.068		
Chemotherapy (yes vs no)	0.280(0.132-0.590)	**0.001**	0.200 (0.046-0.877)	**0.033**
Ascites (yes vs no)	1.984(1.120-3.514)	**0.019**	0.857 (0.291–2.526)	0.780
Metastatectomy (yes vs no)	1.299(0.615-2.744)	0.491		

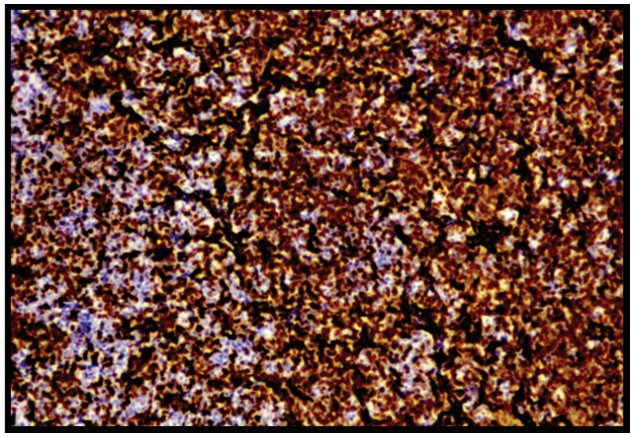

Fig. 2 Histopathological specimen of one patient with colorectal primary showing strong nuclear immunoreactivity with cdx2 (100x).

premenopausal. KT affects a younger age group compared to epithelial ovarian tumors. Increased blood supply in premenopausal ovaries is a factor causing increased hematogenous metastasis to the ovaries in these patients. Many studies have similar findings.[5–9] Thus, whenever a young premenopausal woman is diagnosed with gastrointestinal, gall bladder or pancreatic cancer the status of ovaries also needs to be evaluated.

KT is considered to metastasize to ovary, primarily from gastrointestinal cancers. The majority of studies have implicated either gastric or colorectal malignancies as the most common primary site. Recent reviews have reported a preponderance of colorectal primaries. However, there are reports of this tumor originating from other sites such as carcinomas of gall bladder, pancreas, breast, non hodgkins lymphomas etc.[10] In our study, the most common site was the colorectal region (31%), followed by the stomach (19%). There were many cases from rare sites, such as gall bladder, pancreas, and appendix. The more common presentation of colorectal primaries seems to mirror the greater incidence of colorectal malignancies as compared to the gastric malignancies in India i.e 23.5% (colon 9.1, rectum 14.5) vs 18.5 of the gastrointestinal malignancies.[11]

The primary site of origin was unknown in 8 patients. In the unknown primary patients, a biopsy sample from the enlarged ovarian masses could not be obtained due to an inaccessible location or refusal of consent while in some despite all investigations the primary remained uncharacterized. As a result, the diagnosis of KT was made using a combination of radiological findings that suggested an enlargement of both ovaries, cytological evidence of adenocarcinoma in the ascitic or pleural fluid and raised serum markers that suggested a primary other than the ovary, such as raised CEA in four patients and CA 19.9 in others with normal levels of CA125.

Depending on the primary, the prognosis for KT differs. Studies have indicated that individuals with gastric primary have lower OS rates than those with colorectal malignancies.[12] These patients may also have poor general health and nutritional status and may be at an advanced stage compared to colorectal malignancies. This subgroup, similarly, had a worse survival rate in our patient population, although the difference was not statistically significant.

Although patients with colorectal primary and KT also have a poor prognosis,[13] our patients with CRC primary had statistically significantly better survival than patients at other sites. In comparison to the stomach, pancreas, and other gastrointestinal regions, CRC patients have superior responses to the existing treatments, which results in better survival. Improved operability and survival rates in CRC primary may also be contributing to improved outcome in metastatic disease.Colorectal primary KT were similarly found to have a better prognosis than gastric primary patients in an analysis by Wu et al.[5]

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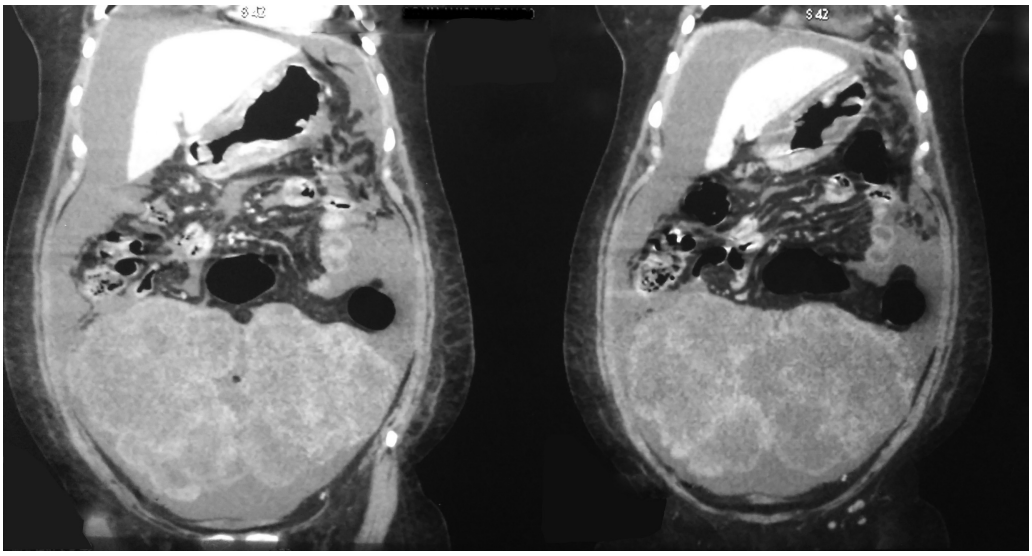

Fig. 3 Coronal CECT image showing presence of two heterogeneously enhancing kissing lesions in lower abdomen and pelvis with non-visualized separate ovaries with associated ascites and thickening of distal body and antero-pyloric region of stomach.

In a review of 57 patients of KT with colorectal primary the individuals had a median survival time of 35 months with a 5year OS of 25%. Complete cytoreductive surgery conferred a significant survival advantage. Just like our study, the use of systemic chemotherapy was associated with a significant survival advantage.[7]

KT patients with a breast cancers primary have also demonstrated to have good survival after treatment,[7] but our study lacked breast cancer primary patients to compare the survival.

In KT no standard treatment protocol has been established thus far. Given that they are an uncommon and diverse category of cancers with unique biological traits and prognoses. As a result, different institutions have distinct therapy protocols. Finding the primary tumor site and the degree of illness dissemination is necessary for managing it. The primary place of origin, pathogenic kind, and degree of metastatic disease all influence KT treatment. Currently, cytoreductive surgery, adjuvant chemotherapy, neoadjuvant chemotherapy, and hyperthermic intraperitoneal chemotherapy (HIPEC) are the viable choices. In the majority of situations, these are utilized in combination. Radical surgery, such as oophorectomies, improve outcomes in only a small number of patients with pelvic-only disease because of the poor outcome and prognosis of these individuals.

The prognosis of KT has been characterized as poor, and they have generally been shown to receive limited benefit from chemotherapeutic agents.[14,15] Majority of our patients received chemotherapy and it improved the OS. The chemotherapy drugs were based on the primary site of the cancer, such as triplets including oxaliplatin, 5-fluorouracil, and leucovorin for CRC[16] and platinum-based chemotherapy regimens for gastric cancer. We employed gemcitabine and cisplatin chemotherapy for pancreatic and gall bladder cancer, platinum-based chemotherapy for gastric cancer, and the FOLFOX regimen for CRC.

The difference in OS between those who received chemotherapy vs those who did not receive it due to any reason was found to be statistically significant. The improved OS with chemotherapy reflects the response to systemic agents, but it is also due to the fact that the patients who were chosen for chemotherapy had better overall health, and patients with poor tolerability would not have been chosen for such treatment.

However, considering the limited benefits of systemic therapy, metastasectomy appears to be the sole beneficial option when the underlying tumor can be completely surgically debulked and removed. A number of studies in both gastric[17] and colorectal[7] primary have shown that patients who had oligometastatic disease benefited from metastasectomy and cytoreductive surgery.

In our study, twenty individuals underwent metastasectomy. It was done in those patients who demonstrated a satisfactory response to treatment at the original location (>50% response rate) and disease limited to the pelvis. The surgical procedures that were employed included unilateral/bilateral adnexectomy or hysterectomy with bilateral adnexectomy. No surgical treatment was administered to 16 patients (44%), either due to additional metastatic lesions or advanced disease, or they were deemed unsuitable candidates for the procedure due to poor general condition at the time of their visit. Given the smaller number of participants in our study, it is possible that the observed survival advantage in patients who underwent metastasectomy did not reach statistical significance. Although we were unable to find any prospective research on the treatment of KTs, the majority of retrospective investigations came to the conclusion that cytoreductive surgeries may aid to increase survival. Their primary location of origin is a factor that should be taken into account before surgery for these patients. When compared to other primary sites, colorectal primaries are regarded as the finest surgical prospects.[5,18] Greater operability and better survival rates in CRC primary

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may be contributing to enhanced outcome in metastatic disease.

Another factor worth considering when analyzing results involving surgery is that patients undergoing the procedure are typically those who possess a good general condition. Meanwhile, patients with poor health and aggressive disease are only considered for palliative systemic agents. This skews the results of retrospective studies in favor of surgery.

HIPEC and chemotherapy have both been shown to improve outcomes in KT.[19] Cytoreductive surgery has also been demonstrated to have a significant influence on OS when combined with HIPEC, but in our institution, HIPEC had not been used.

In a review of 20 retrospective studies, it was seen that cytoreductive surgery was the best in improving OS in KT patients. There were found to be contradicting results regarding the benefit of chemotherapy. Where HIPEC was used, it seemed to be more effective, either alone or in conjunction with cytoreductive surgery. The benefit of neoadjuvant CT was obscure.[9]

Bilateral ovarian involvement should raise the suspicion of metastasis. Around 10% of bilateral ovarian tumors are metastatic; however, many metastatic tumors are also unilateral, as seen in 25% of cases in our study. The bilateral tumors with endometriod-like and mucinous features should be suspected of metastatic disease.[20]

In the current investigation, there was no relationship between survival, bi-laterality, or tumor size. it could signal that ovarian metastasis is a sign of an aggressive disease since even if a tumor is little in size, it portends poor prognosis. Additionally, the prognosis is unaffected by peritoneal dissemination, which may frequently be bilateral or less frequently unilateral. Even though synchronous metastasis is associated with poor mortality and is an adverse factor[5]; the prognosis for the synchronous and metachronous disease was the same in our study,

Numerous studies have found a strong correlation between ascites and poor survival, and our findings corroborated these studies.[5,21] In patients with KT, ascites is either due to peritoneal invasion by the malignancy or due to malnourishment, it is an aggressive illness with widespread peritoneal dissemination, which has poor prognoses.

The differentiation from primary epithelial ovarian cancers is also of utmost importance because this malignancy is sensitive to chemotherapy and has a better survival. A recent review has incorporated clinical and radiographic features to differentiate KTs from primary epithelial ovarian tumors.[22] Our study's findings suggest that chemotherapy significantly increased our study population's survival. Newer treatment regimens and targeted therapy are being tested, and they will undoubtedly affect survival in the future.[23–25] OS time is influenced by the site of origin of the primary tumor which was also noted in our study.

This study has a lot of flaws It is retrospective in nature and has a small sample size. This data comes from just one institution The rarity of KT has precluded prospective trials in this entity throughout the globe and reporting and pooling of this data is essentially required.

This study, however, is the first to show the clinical traits and survival rates in the sub-Himalayan population. The results of this study shed light on the features of this tumor in our sample of patients, and they can be used to identify people in a pool who might benefit from intensive treatment and have a higher chance of survival. Additionally, we are aware that chemotherapy, particularly in cases of extensive disease, can increase survival in these patients and should be offered. The role of cytoreductive surgery and newer combination regimens need to be explored further and patients with disease limited to pelvis may be candidates for surgery. Though, uniformity in treatment of KT is a difficult and less attainable task, multi-institutional studies including a sizable patient population may offer more accurate prognostic data and help develop future treatment guidelines for this understudied illness.

Conflict of Interest

None declared.

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