Diplomarbeit

Pre-treatment lymphocyte-monocyte ratio (LMR) as a potential prognostic factor in a cohort of patients with upper tract urothelial carcinoma

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Nikita Sobolev

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Doktor der gesamten Heilkunde
(Dr.med.univ.)

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Priv.-Doz.Dr.med.univ. Georg C. Hutterer

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Eidesstattliche Erklärung

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Graz, am 28.07.2014 Sobolev Nikita

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Besonderheit

Die vorliegende Diplomarbeit wurde von mir auf eigenen Wunsch hin in Englischer Sprache abgefasst.

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Abbreviations and acronyms

UTUC = upper tract urothelial carcinoma

CSS = cancer-specific survival

HNPCC = hereditary non-polyposis colorectal carcinoma

CIS = carcinoma *in situ*

TNM = Tumour Node Metastasis

WHO = World Health Organization

CT = computed tomography

MRI = magnetic resonance imaging

FISH = fluorescence *in situ* hybridization

RNU = radical nephroureterectomy

ASA = American Society of Anesthesiologists

ECOG = Eastern Cooperative Oncology Group

OS = overall survival

LND = Lymph node dissection

LMR = lymphocyte-monocyte ratio

ROC = receiver-operating curve

HR = hazard ratio

CI = confidence interval

TAM = tumour-associated macrophages

EBM = evidence based medicine

EAU = European Association of Urology

GR = grade of recommendation

HIF = hypoxia-inducible factor

MSIs = microsatellite instabilities

Summary

Objectives: To investigate the potential prognostic impact of the lymphocyte-monocyte ratio (LMR) in a large European cohort of localized upper urinary tract urothelial carcinoma (UTUC) patients. The LMR as an indicator of systemic inflammatory response has been shown to represent a potential prognostic factor in various types of human cancers. Up to date, the prognostic significance of the LMR in UTUC has not been evaluated yet.

Materials and methods: Clinico-pathological data from 182 non-metastatic UTUC patients, operated between 1990 and 2012 at a single tertiary academic center, were evaluated retrospectively. Pre-treatment LMR was assessed one day before surgery. Patients were categorized using a LMR cut-off value of 2.0 according to a calculation by receiver-operating curve analysis. Patients' overall survival (OS) was assessed using the Kaplan-Meier method. To evaluate the independent prognostic significance of the LMR, a multivariate proportional Cox regression model was applied for OS.

Results: In multivariate analyses, age at the date of surgery (<65 *vs.* ≥65yrs., HR=2.10, 95%CI=1.22-3.64, *p*=0.008), pathologic T-stage (pT1 *vs.* pT2-4, HR=2.15, 95%CI=1.26-3.67, *p*=0.005), as well as the LMR (<2 *vs.* ≥2, HR=0.56, 95%CI=0.35-0.92, *p*=0.021) were independent predictors of UTUC patients' OS.

Conclusions: In the cohort studied, patients with an elevated (≥2) pre-operative LMR had a subsequently longer OS after radical surgery for UTUC, compared to those with a low (<2) pre-operative LMR. Thus, we believe this parameter might be considered an additional prognostic factor in UTUC in the future.

1. Epidemiology of upper urinary tract urothelial carcinoma

Urothelial carcinomas are the fourth most common tumours after prostate (or breast), lung and colorectal cancer.[1-5] They can be located in the lower (bladder and urethra) or upper urinary tract (pyelocaliceal cavities and ureter). Bladder tumours account for 90-95% of urothelial carcinomas and are the most common malignancy of the urinary tract.[1-5] However, upper urinary tract urothelial carcinomas (UTUCs) are relatively uncommon and account for only 5-10% of urothelial carcinomas.[4,6] The estimated annual incidence of UTUCs in western countries is about two new cases per 100,000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present.[7] Recurrence of disease in the bladder occurs in 22-47% of UTUC patients[8-10], whereas recurrence in the contralateral upper tract is observed in 2-6%.[11,12]

The natural history of UTUC differs from that of bladder cancer: 60% of UTUCs are invasive at diagnosis compared with only 15-25% of bladder tumours.[13,14] At present, patients' reported 5-year cancer-specific survival (CSS) rates achieve 50% for locally muscle invasive tumours and less than 10% for advanced stages of the disease.[13] UTUCs have a peak incidence in patients in their 70s and 80s and they are three times more prevalent in men than in women.[15,16] There are familial/hereditary cases of UTUCs linked to hereditary non-polyposis colorectal carcinoma (HNPCC).[17] Among UTUC patients, HNPCC cases can be screened during a medical interview.[18] There is a suspicion of hereditary UTUC if the patient is < 60 years of age, has a personal history of a HNPCC-associated cancer, a first-degree relative aged < 50 years with HNPCC-associated cancer, or two first-degree relatives with HNPCC-associated cancer.[18] These patients should undergo DNA sequencing to identify hereditary cancers that have been misclassified as sporadic cancers by insufficient

clinical data.[19] The presence of other HNPCC-associated cancers should also be evaluated. These patients should be closely monitored, and genetic counselling is advocated.[17,19]

2. Risk factors for upper urinary tract urothelial carcinoma

Several environmental factors contribute to the development of UTUC.[20,21] Some are similar to those associated with bladder cancer, whereas others are more specific for UTUC. Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Exposure to tobacco increases the relative risk of developing UTUC from 2.5 to 7.[20,21] UTUC "amino tumours" are related to occupational exposure to certain aromatic amines. These aromatic hydrocarbons are used in many industries (e.g., dyes, textiles, rubber, chemicals, petrochemicals, and coal). They are responsible for the carcinogenicity of certain chemicals, including benzidine and β-naphthalene. These two chemicals have been banned since the 1960s in most industrialised countries. In most cases, UTUCs are secondary to an amino tumour of the bladder. The average duration of exposure needed to develop a UTUC is approximately 7 years, with a latency period of about 20 years following the termination of exposure. The estimated risk (odds ratio) of developing UTUC after exposure to aromatic amines is 8.3.[21,22] Upper urinary tract tumours resulting from phenacetin consumption almost disappeared after the product was banned in the 1970s.[21] Although the incidence of Balkan endemic nephropathy is also on the decline, roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the pathophysiology and induction, respectively, of this nephropathy.[23-26] Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis* (plants endemic to the Balkans). This acid contains a set of highly toxic nitrophenolate derivatives that exhibit a powerful mutagenic action due to their ability to make up covalent links with cell DNA. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139. This mutation is very rare in the non-

exposed population and is predominant in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy who present with UTUC.[21,23,24] A relatively high incidence of UTUC has also been described in Taiwan, especially in the population on the southwest coast of the island, and currently represents 20-25% of urothelial carcinomas in the region.[21,24] The association of UTUC with blackfoot disease and arsenic exposure remains unclear in this patient population.[21,24] Differences in the ability to counteract carcinogens may contribute to host susceptibility and the risk of developing urothelial carcinoma. Although it is not unusual that a genotype confers protection for an organ and increases the risk for another, UTUC may share some risk factors or molecular disruption pathways with bladder urothelial carcinoma, but each has it‘s own specific features. Certain genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, thus, there is variability in inter-individual susceptibility to the risk factors mentioned. Only two polymorphisms specific to UTUC have been reported so far.[27,28] A variant allele, SULT1A1*2, which reduces sulfotransferase activity, and a polymorphism located at the T allele of rs9642880 on chromosome 8q24 enhance the risk of developing UTUC.

3. Histologic classification of upper urinary tract urothelial carcinoma

Histologic UTUC subtypes

More than 95% of urothelial carcinomas are derived from the urothelium and correspond to UTUCs or bladder tumours.[13,29] With regard to UTUC, morphological variants have been described that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours, and such carcinomas are associated with one of the following variants: micropapillary, clear cell, neuroendocrine, and lymphoepithelial.[29,30] Collecting-duct carcinoma has similar characteristics as UTUC because of it‘s common embryologic origin.[31] Upper urinary tract tumours with pure non-urothelial histology are exceptions[32,33] but a variant can be seen in nearly 25% of cases.[34] Squamous cell carcinomas of the upper urinary tract represent < 10% of pyelocaliceal tumours and are even rarer within the ureter. Squamous cell carcinoma of the urinary tract is associated with chronic inflammatory and infectious disease arising from stones in the urinary tract.[29,30] Other histological subtypes are adenocarcinomas (< 1%), small cell carcinomas and sarcomas.

Histopathological classification

The classification and morphology of UTUCs are similar to those of bladder carcinomas.[13] It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential, lowgrade papillary, high-grade papillary), flat lesions (carcinoma *in situ* [CIS]), and invasive carcinomas. All variants of urothelial tumours described in the bladder can also be observed in the upper urinary tract.[34]

Tumour Node Metastasis (TNM) staging

The table below presents the Union Internationale Contre le Cancer (UICC) 2009 Tumour Node Metastasis (TNM) classification used throughout international guidelines.[35] According to the TNM classification system, the regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect the N classification. There is an interest to use a renal pelvic pT3 subclassification to discriminate between microscopic infiltration of the renal parenchyma (pT3a) vs. macroscopic infiltration or invasion of peripelvic adipose tissue (pT3b).[34,36] pT3b UTUCs are more likely to have aggressive pathological features and have a higher risk of recurrence.[34,36] **TNM classification 2009 for UTUC (35)*:**

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	CIS
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma
	(Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

**All EAU guidelines advocate the TNM system of tumour classification.*

Tumour grading

Until 2004, the most common classification used was the World Health Organization (WHO) classification of 1973, which distinguished only three grades (G-1, G-2 and G-3).[37] In recent years, molecular biological data have allowed for further distinction between different tumour groups and the development of a new classification system that better reflects the potential growth of these tumours.[38] Thus the 2004 WHO classification now takes histological data into account to distinguish among three groups of non-invasive tumours: papillary urothelial neoplasia of low malignant potential; low-grade carcinomas; and high-grade carcinomas. Almost no tumours of low malignant potential are reported in the upper urinary tract.[29,30]

4. Diagnosis of upper urinary tract urothelial carcinoma

Computed tomography urography

Computed tomography (CT) urography is the imaging technique with the highest diagnostic accuracy for UTUC and has replaced intravenous excretory urography and ultrasonography as the first-line imaging test for investigating high-risk patients.[40] The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99 depending on the technique used.[43-50] Computed tomography urography of the urinary tract acquires at least one image series during the excretory phase, usually 10-15 min, following the administration of intravenous contrast medium.[51] Rapid acquisition of thin sections allows high-resolution isotropic images to be produced that can be viewed in multiple planes to assist with diagnosis without degradation of resolution.[52,53] Computed tomography urography can also detect wall thickening of the renal pelvis or ureter, which can represent a sign of UTUC, even when there is no luminal mass effect, but flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening.[54] The secondary sign of hydronephrosis on imaging in the presence of UTUC is associated with advanced pathological disease and poorer oncological outcomes.[51,55]

Magnetic resonance imaging

Magnetic resonance (MRI) urography is indicated in patients who cannot undergo CT urography usually when radiation or iodinated contrast media are contraindicated.[56] The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm.[56] Magnetic resonance urography with certain gadolinium-based contrast media is contraindicated in select patients with severe renal impairment (< 30 ml/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis. Computed

tomography urography is generally preferred to MR urography for diagnosing UTUC in terms of greater diagnostic accuracy, lower cost, and greater patient acceptability.

Cystoscopy and urinary cytology

Positive urine cytology is highly suggestive of UTUC when bladder cystoscopy is normal and if CIS of the bladder or prostatic urethra has been largely excluded (e.g., by biopsies of any suspicious lesion, possibly guided by photodynamic diagnosis).[13,57] Cytology is less sensitive for UTUC than for bladder tumours, even for high-grade lesions, and it should ideally be performed *in situ* (i.e., in the renal cavities).[58] Retrograde ureteropyelography (through a ureteral catheter or during ureteroscopy) remains an option for the exclusion of a tumour in the upper urinary tract.[44,59] However, urinary cytology of the renal cavities and ureteral lumina should preferably be performed prior to application of larger amounts of contrast agent for retrograde ureteroand pyelography, because it may deteriorate cytological specimens. The sensitivity of fluorescence *in situ* hybridisation (FISH) for the identification of molecular abnormalities characterising UTUCs parallels its performance in bladder cancer; however, the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally-invasive therapy for UTUCs may limit its usefulness.[60,61] In addition, FISH appears to have limited value for upper UTUC surveillance.[60,61]

Diagnostic ureteroscopy

Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis and collecting system with a technical success approaching 95%. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate regardless of the size of the sample.[62] Undergrading may occur from the diagnostic

biopsy, making intensive follow-up a requirement if renal sparing treatments are selected.[63] Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ*.[59,64,65] Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, when conservative treatment is being considered, or in patients with a solitary kidney. If available, ureteroscopy and biopsy should be performed in the preoperative assessment of any UTUC patient. Combining ureteroscopic biopsy grade, diagnostic imaging findings such as hydronephrosis, and urinary cytology may help decision making on radical nephroureterectomy (RNU) *vs.* endoscopic treatment.[64,66] Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions. Narrow band imaging appears to be the most promising technique but results are still preliminary.[66,67] The table below lists the recommendations:

EAU-Guidelines for the diagnosis of UTUC

Recommendations	GR
Urinary cytology	A
Cystoscopy to rule out a concomitant bladder tumour	A
CT urography	A
Diagnostic ureteroscopy and biopsy	C
Retrograde ureteropyelography	C

5. Prognostic factors in upper tract urothelial carcinoma

UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-year CSS is < 50% for pT2/pT3 and < 10% for pT4.[67,68] This section briefly describes the currently recognised prognostic factors.[69]

Tumour stage and grade

According to the most recent classifications, the primary recognised prognostic factors are tumour stage and grade.[64,69-71] Extranodal extension appears to be a powerful predictor of clinical outcomes in patients with UTUC and positive lymph node metastases.[72]

Age and sex

Sex is no longer considered an independent prognostic factor that influences UTUC mortality.[15,69,73] Conversely, patient‘s age is still considered an independent prognostic factor because older age at the time of RNU is associated with decreased CSS.[69,74] However, chronologic age alone should not be an absolute exclusion criterion for the treatment of potentially curable UTUC but rather overall life expectancy. A significant proportion of elderly patients can still be cured with RNU.[74] This suggests that chronological age alone is an inadequate indicator of outcomes in older UTUC patients.[74,75]

Ethnicity

There are differences in clinicopathological characteristics of tumours between Caucasian and Japanese patients. However, race and ethnicity are not so far recognised as independent factors for survival.[76]

Tumour location

According to the most recent findings, the initial location of the tumour within the upper urinary tract (e.g., ureter *vs.* renal pelvis) is a prognostic factor.[77-79] There is a prognostic impact of tumour location when adjusted for tumour stage: ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours.[69,78-80]

Tobacco consumption

Smoking intensity (long-term exposure) and being a smoker at diagnosis increases the risk for poor oncological outcomes.[81-83]

Lymphovascular invasion

Lymphovascular invasion is present in approximately 20% of UTUCs and an independent predictor of survival.[84,85] Lymphovascular invasion status should be systematically included and specifically reported in the pathologic report of all RNU specimens.[84,86]

Surgical margins

Positive surgical margins after RNU appear to be a significant factor for developing subsequent UTUC metastases. Pathologists should look for, and report on, positive margins at the level of ureter transsections, bladder cuff and around the tumour if the tumour is > T2.[87]

Other factors

Extensive tumour necrosis is an independent predictor of clinical outcomes in patients who undergo RNU. Extensive tumour necrosis can be defined as > 10% of the tumour area.[88,89] The tumour architecture (e.g., papillary vs. sessile) of UTUCs

appears to be associated with the prognosis after RNU. A sessile growth pattern is associated with the worst outcomes.[90,91]

The presence of concomitant CIS in patients with organ-confined UTUC is associated with a higher risk of recurrent disease and cancer-specific mortality.[92,93] Similar to lower tract urothelial carcinoma, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease.[94] A previous history of bladder CIS is associated with increased risk of recurrence and death from UTUCs.[95] The American Society of Anesthesiologists (ASA) score also significantly correlates with CSS after RNU[96] albeit Eastern Cooperative Oncology Group (ECOG) performance status correlates only with overall survival (OS).[122] Obesity and higher body mass index adversely affect cancer-specific outcomes in patients with UTUC.[98]

6. Symptoms of upper urinary tract urothelial carcinoma

The diagnosis of UTUC may be fortuitous or related to the exploration of symptoms. Symptoms are generally restricted.[39] The most common symptom of UTUC is gross or microscopic haematuria (70-80%).[40] Flank pain occurs in 20-40% of cases and a lumbar mass is present in 10-20%.[41,42] However, systemic symptoms (altered health condition including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt consideration of a more rigorous metastatic evaluation.[41,42]

7. Treatment modalities in upper urinary tract urothelial carcinoma

Localised disease:

Radical nephroureterectomy

Radical nephroureterectomy (RNU) with excision of the bladder cuff is considered to represent the gold standard treatment for UTUC, regardless of the location of the tumour in the upper urinary tract.[14] The RNU procedure must comply with oncological principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection.[14] Resection of the distal ureter and it‘s orifice is performed because it is a part of the urinary tract with considerable risk of tumour recurrence. After removal of the proximal part, it is almost impossible to image or approach it by endoscopy during follow-up. Recent publications on survival after RNU have concluded that removal of the distal ureter and bladder cuff is beneficial.[108-110] McDonald *et al*. presented the pluck technique in 1952, but it was not until 1995[111] that the usefulness of an endoscopic approach to the distal ureter was emphasised, and then several other alternative techniques were reconsidered to simplify resection of the distal ureter: stripping, transurethral resection of the intramural ureter, and intussusception techniques.[11,109] Apart from ureteral stripping, none of these techniques is inferior to excision of the bladder cuff.[74-76,78] Nevertheless, the endoscopic approach is clearly associated with a higher risk of subsequent bladder recurrence.[112] A delay between diagnosis and removal of the tumour may increase the risk of disease progression. However the cut-off has been disputed between 45 days and 3 months and it remains a moot point.[113-115] Lymph node dissection (LND) associated with RNU is of therapeutic interest and allows for optimal staging of the disease.[116,117] However, the anatomical sites of LND have not

yet been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed.[118] Lymph node dissection appears to be unnecessary in cases of TaT1 UTUCs because it was reported to be retrieved in 2.2% pT-1 *vs.* 16% pT-2-4 tumours.[117] In addition, a continuous increase in the probability of lymph-node-positive disease related to pT-classification has been described.[117] However, these data are retrospective; consequently, under-reporting of the true rate of node-positive disease is likely. It is not yet possible to standardise either indication or extent of LND. However, LND can be achieved according to lymphatic drainage as follows: LND medially to the ureter in ureteropelvic tumour, retroperitoneal LND in case of higher ureteral tumour and/or tumour of the renal pelvis (i.e., right side: border vena cava and left side: border aorta).[116-118] The laparoscopic RNU has not yet achieved final proof of its safety. There are early reports of retroperitoneal metastatic dissemination and dissemination along the trocar pathway when large tumours were manipulated in a pneumoperitoneal environment.[119,120] Several precautions must be taken when operating with a pneumoperitoneum because it may increase tumour spillage:

• Entering the urinary tract should be avoided.

• Direct contact of the instruments with the tumour should be avoided.

• Laparoscopic RNU must take place in a closed system. Morcellation of the tumour should be avoided, and an endobag is necessary to extract the tumour.

• The kidney and ureter must be removed en bloc with the bladder cuff.

• Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU, until proven otherwise.

Recent data show a tendency towards equivalent oncological outcomes after either laparoscopic or open RNU.[121-126] In addition, the laparoscopic approach appears to be superior to open surgery only with regard to functional outcomes.[121-126] Only one prospective randomised study of 80 patients has provided evidence that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC.[127] In addition, it has been demonstrated that oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements.[128] Recommendations according tot he recent EAU-Guidelines are listed in the table below:

Guidelines for radical management of UTUC: RNU

Indications for RNU for UTUC	**GR**
Suspicion of infiltrating UTUC on imaging	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Non-invasive but large (i.e. > 2 cm) UTUC	B
Techniques for RNU for UTUC	
Open and laparoscopic access are equivalent in terms of efficacy	B
Bladder cuff removal is imperative	A
Several techniques for bladder cuff excision are acceptable, except stripping	C
Lymphadenectomy is recommended in case of invasive UTUC	C
Postoperative instillation (chemotherapy) is recommended after RNU to avoid bladder recurrence	B

Conservative surgery

Conservative surgery for low-risk UTUC allows preservation of the upper urinary renal unit while sparing the patient the morbidity associated with open radical surgery. Conservative management of UTUC can be considered in imperative cases (renal insufficiency or solitary functional kidney) or in elective cases (when the contralateral kidney is functional) for low-grade, low-stage tumours.[110,129,130] The

choice of technique depends on technical constraints, the anatomical location of the tumour, and the experience of the surgeon.

Ureteroscopy

Endoscopic ablation can be considered in highly select cases and in these situations[131-133]:

• A flexible rather than a rigid ureteroscope, laser generator[134], and pliers (pluck) for biopsies are available.[132,135]

• The patient is informed of the need for closer, more stringent surveillance.

• A complete resection of the tumour is strongly advocated.

However there is a risk of understaging and undergrading the disease with pure endoscopic management.

Segmental resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Ureteroureterostomy is indicated for non-invasive, low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means (i.e., size or multiplicity) and for high-grade or invasive tumours when renal sparing surgery for preservation of renal function is a goal. High-grade tumours of the proximal ureter or midureter should undergo RNU with excision of bladder cuff when possible. Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means (i.e., size or multiplicity) and for high-

grade, locally-invasive tumours.[136-138] For both ureteroureterostomy and complete distal ureterectomy and neocystostomy it is necessary, however, to ensure that the area of tissue around the tumour is not invaded. Segmental resection of the iliac and lumbar ureter is associated with a failure rate greater than that for the distal pelvic ureter.[136-138] Open resection of tumours of the renal pelvis or calices has almost disappeared. Resection of pyelocaliceal tumours is technically difficult, and the recurrence rate is higher than for tumours of the ureter.

Percutaneous access

Percutaneous management can be considered for low-grade or non-invasive UTUC in the renal cavities.[132,139,140] This treatment option may be offered to patients with low-grade tumours in the lower caliceal system that are inaccessible or difficult to manage by ureteroscopy. A theoretical risk of seeding exists in the puncture tract and in perforations that may occur during the procedure. This approach, however, is being progressively abandoned due to enhanced materials and advances in distal-tip deflection of recent ureteroscopes.[132,139,140]

Adjuvant topical agents

The antegrade instillation of bacillus Calmette-Guérin vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete erradication of the tumour) is technically feasible after conservative treatment of UTUC or for the treatment of CIS.[141] Retrograde instillation through a ureteric stent or with the help of the reflux obtained from a double J stent have also been used[142], but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The medium-term results are similar to those observed for the treatment of bladder tumours but have

not been confirmed in long-term studies.[141,142] One prospective randomised study of 144 patients has provided evidence that a single postoperative dose of intravesical mitomycin reduces the risk (i.e., absolute risk 11%) of a bladder tumour within the first year following RNU.[143] The table below lists the recommendations:

EAU-Guidelines for conservative management of UTUC

Indications for conservative management of UTUC	**GR**
Unifocal tumour	B
Tumour size less than 1 cm	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on CT urography	B
Understanding of close follow-up	B
Techniques used in conservative management of UTUC	
Laser should be used in case of endoscopic treatment	C
Flexible ureteroscopy is preferable over rigid ureteroscopy	C
A percutaneous approach remains an option in small low-grade caliceal tumours unsuitable for ureteroscopic treatment	C
Ureteroureterostomy is indicated for non-invasive low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means, and for high-grade or invasive tumours when RSS for preservation of renal function is a goal	C
Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means and for high-grade, locally-invasive tumours	C

Advanced disease:

Nephroureterectomy

There are no benefits of RNU in metastatic (M+) disease, although it can be considered a palliative option.[14,117]

Chemotherapy

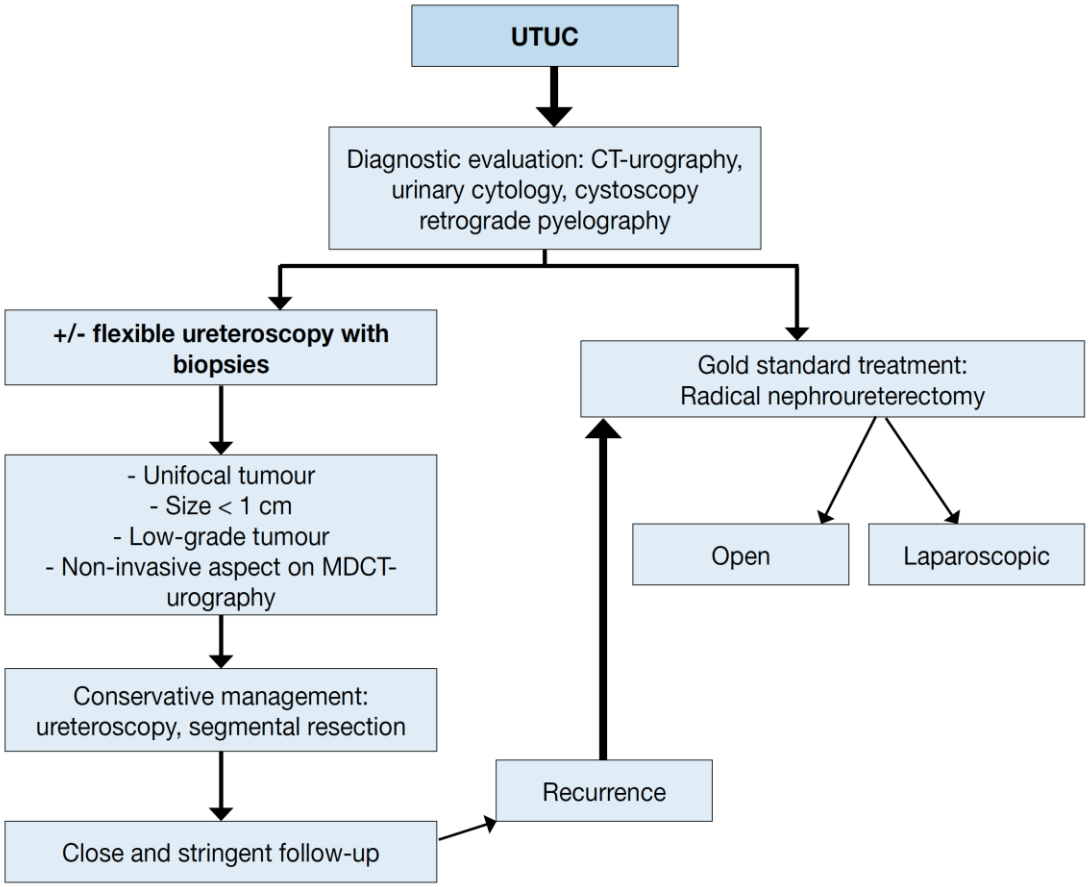
UTUCs are urothelial tumours, therefore, platinum-based chemotherapy is expected to produce similar results to those seen in bladder cancer. Several platinum-based chemotherapy regimens have been proposed.[144] However, adding chemotherapy-

related toxicity, particularly nephrotoxicity from platinum derivatives, to a population with already impaired postsurgical renal function may also be related to the reduced survival in these patients.[145,146] In addition, not all the patients receive this treatment because of comorbidity and impaired renal function after radical surgery. Contrary to what has been demonstrated for bladder cancer, there have been no reported effects of neoadjuvant chemotherapy for UTUCs in the only study published to date.[147] Although survival data need to mature and longer follow-up is awaited, current preliminary data provide justification for the sustained support of trials using this strategy in UTUC. Adjuvant chemotherapy can somehow achieve a recurrence-free rate of up to 50% but has clearly no impact on survival.[148,149] Further data are awaited from the ongoing prospective randomised POUT trial (PeriOperative chemotherapy or sUrveillance in upper Tract urothelial cancer).[150] Data are currently insufficient to provide any recommendations.

Radiotherapy

Adjuvant radiotherapy may improve local control of the disease.[151] When given in combination with cisplatinum, it may result in longer disease-free and overall survival.[152] Radiotherapy appears to be scarcely relevant nowadays both as a unique therapy and associated with chemotherapy as adjuvant therapy:

Proposed flowchart for the management of UTUC according to EAU-Guidelines



8. Follow-up strategies

Stringent follow-up of UTUC patients after surgical treatment is mandatory to detect metachronous bladder tumours (in all cases), local recurrence, and distant metastases (in the case of invasive tumours). When RNU is performed, local recurrence is rare, and the risk of distant metastases is directly related to the risk factors listed previously. The reported recurrence rate within the bladder after treatment of a primary UTUC varies considerably from 22 to 47%.[8,10] Thus, the bladder should be observed in all cases. The surveillance regimen is based on cystoscopy and urinary cytology for at least 5 years.[8-10] Bladder recurrence should not be considered as distant recurrence. When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence.[129,133,135] Despite notable improvements in endourological technology, the follow-up of patients treated with conservative therapy is difficult, and frequent and repeated endoscopic procedures are necessary. The table below lists the recommended follow-up schedules:

EAU-Guidelines for follow-up of UTUC patients after initial treatment

After RNU, over at least 5 years	**GR**
Non-invasive tumour	
Cystoscopy/urinary cytology at 3 months and then yearly	C
CT every year	C
Invasive tumour	
Cystoscopy/urinary cytology at 3 months and then yearly	C
CT urography every 6 months over 2 years and then yearly	C
After conservative management, over at least 5 years	
Urinary cytology and CT urography at 3 and 6 months, and then yearly	C
Cystoscopy, ureteroscopy and cytology *in situ* at 3 and 6 months, and then every 6 months over 2 years, and then yearly	C

9. Introduction

Pathologic T-stage and tumour grade are currently regarded to represent the most important pathological prognostic factors in UTUC.[153,154] Additionally, the presence of lymphovascular invasion, as well as of histologic tumour necrosis have been demonstrated to represent independent predictors of UTUC patients' survival.[155,156] Recently, the potential prognostic significance of pre-operatively available factors in UTUC patients, which is still limited, is receiving great interest. The identification of risk factors that are able to accurately predict the clinical outcome of UTUC patients is paramount, since they would allow the assessment of patients' individualised risk profiles. Several groups of authors developed pre-, as well as post-operative prognostic models to better predict UTUC patients' clinical outcomes.[154,157] For instance, Margulis *et al.* integrated patients' disease-related symptoms, histologic subtype, tumour size, as well as pathologic T-stage into a pre-treatment multivariable prognostic model to predict non-organ confined UTUC.[157]

There is a growing body of evidence suggesting that an interactive relationship between haemostatic factors and tumour biology might play a pivotal role in human cancer development, as well as in metastatic tumour spread.[158-166] Several markers of systemic inflammatory response, such as C-reactive protein, plasma fibrinogen, the neutrophil-lymphocyte ratio, as well as the derived neutrophil-lymphocyte ratio have been shown to represent independent prognosticators in various human cancers.[158-166] In localized UTUC, to the best of our knowledge, data regarding the potential prognostic value of the pre-treatment lymphocyte-monocyte ratio (LMR) are not published yet. Thus, the aim of the recent study was to clarify the potential prognostic value of the pre-operatively assessed LMR in a large cohort of localised UTUC patients originating from central Europe.

10. Materials and methods

This retrospective analysis included data from 182 non-metastatic UTUC patients who underwent RNU or in select cases segmental ureterectomy at the Department of Urology at the Medical University of Graz between September 1990 and July 2012. All clinico-pathological data were retrieved from medical records from the Department of Urology, as well as from pathology reports from the Institute of Pathology at the same institution. In all cases the diagnosis (localised non-metastatic UTUC) was established by radiologic imaging, eg. CT or MRI, cystoscopy, urinary cytology and/or ureteroscopy with multiple biopsy sampling. Segmental ureterectomy was conducted in imperative (solitary kidney, chronic renal insufficiency, impaired renal function or parenchymal rarification of the contralateral kidney or ASA 4) or in elective cases (lesion restricted to the distal ureter). Pathologic T-stages were uniformely adjusted according to the TNM classification system 2009, tumour grade was assessed according to WHO 1973.[167] Tumour site and location, presence or absence (not quantitatively assessed) of histologic coagulative tumour necrosis, surgical resection margins, as well as patients' age and gender were retrieved from patients' medical/pathological records. Lymphovascular invasion was defined as the presence of tumour cells within the endothelial space without underlying muscular wall. Analyses of the laboratory data, including lymphocyte and monocyte counts, were routinely performed one day before surgical intervention. Patients' post-operative surveillance included physical examination, performance of cystoscopy and urinary cytology for at least 5 years and was performed according to the current EAU Guidelines for the follow-up of UTUC patients after initial treatment.[168] Radiographic evaluation of the contralateral upper urinary tract using CT or MRI was performed every 6 months for the first 2 years and once a year afterwards. No neoadjuvant or

adjuvant treatment was administered. Dates of death were obtained from the central registry of the Austrian Bureau of Statistics. Survival data were retrieved from the electronic patient records at the Medical University of Graz, as well as from electronic patient records of any other accessible hospital in the district of Styria. Missing data were obtained using letters and telephone interviews with patients and/or patients' general practitioners involved. Patients' death was assessed as either cancer-related or unrelated. All deaths of patient's who had confirmed metastatic UTUC at any time during follow-up, were considered to be cancer-related. All other deaths were considered as other cause mortality. Cancer-specific survival was defined as the time (in months) from the date of surgery to cancer-related death. Overall survival was defined as the time (in months) from the date of surgery to patients' death of any cause. The study was approved by the local ethical committee of the Medical University of Graz.

Statistical analysis

Overall survival represented the primary study endpoint and was calculated from the date of surgery to patients' death of any cause. The ideal cut-off value for the continuously coded LMR was calculated by applying a receiver-operating curve (ROC)-analysis to test all possible cut-offs that would discriminate between patients' survival and cancer-related death, as previously described.[164] The relationship between the LMR and patients' clinico-pathological parameters was studied by non-parametric tests (χ^2-test and Mann-Whitney's *U*-test). Patients' clinical endpoints were calculated using the Kaplan-Meier method and were compared by the log-rank test. Backward stepwise multivariable Cox proportional analyses were performed to determine the influence of pathologic T-stage, tumour grade, patients' age, gender, as well as histologic tumour necrosis on OS. Hazard ratios (HRs) estimated from the

Cox analyses were reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). A two-sided $p<0.05$ was considered statistically significant.

11. Results

Of the 182 consecutive UTUC patients, 111 (61.0%) were male and 71 (39.0%) were female. The mean age of the study cohort at the time of surgery was 69.0 ± 10.3 (range 32-89) yrs. In 100 (54.9%) cases the tumour was located in the renal pelvis and in 82 (45.1%) cases in the ureter. Pathologic T-stages were classified as pT-1 in 83 (45.6%) and pT-2-4 in 99 (54.4%) patients. Tumour grades were distributed as G-1+G-2 in 99 (54.4%) and as G-3+G-4 in 83 (45.6%) cases. Overall, the presence of histologic coagulative tumour necrosis was noted in 24 (13.2%) patients, a mean monocyte count of 0.67±0.32, a mean lymphocyte count of 1.48±0.59 and a median pre-treatment LMR of 1.76±0.43 (s. Table 1). Regarding the UTUC study cohort, a cut-off value of 2.0 for the LMR was determined to be optimal, which prompted us to select this cut-off value for all subsequent analyses. Accordingly, we defined a low (<2.0) and high (≥2.0) LMR group. Overall, there were 139 (76.4%) patients with a high pre-operative LMR and 43 (23.6%) patients with a low pre-operative LMR. The association of the LMR with various clinico-pathological parameters in the study cohort is shown in Table 2. Regarding OS, an elevated pre-operative LMR (≥2.0) was statistically significantly associated with a lower overall mortality (40.3% *vs.* 60.5% deaths) than below the cut-off value (p<0.001) [s. Fig. 1]. In univariable analysis, age at operation (<65 *vs.* ≥65 yrs., p=0.005), tumour location (ureter *vs.* pelvis, p=0.040), pathologic T-stage (pT-1 *vs.* pT-2-4, p<0.001), tumour grade (G-1+G-2 *vs.* G-3+G-4, p<0.001), the presence of histologic tumour necrosis (no *vs.* yes, p<0.001), as well as an elevated pre-operative LMR (<2 *vs.* ≥2, p=0.020) were statistically significantly associated with longer OS (s. Table 3). To determine the independent prognostic significance of the pre-operative LMR for patients' OS, a multivariate analysis using a Cox proportional hazard model was performed. It demonstrated that age at operation

(<65 *vs.* ≥65 yrs., HR=2.10, 95%CI=1.22-3.64, *p*=0.008), pathologic T-stage (pT-1 *vs.* pT-2-4, HR=2.15, 95%CI=1.26-3.67, *p*=0.005), as well as the pre-operative LMR (<2 *vs.* ≥2, HR=0.56, 95%CI=0.35-0.92, *p*=0.021) were independent predictors of OS (s. Table 3).

12. Discussion

Despite enormous progress in the identification of genetic and molecular alterations in UTUC, including gene mutations, non-coding RNA expression, as well as chromosomal aberrations, has been achieved over the last years[169,170], the routine prognostic risk assessment of UTUC patients currently still relies on well-established clinico-pathological prognostic variables, such as pathologic T-stage and tumour grade.[153,154] Within the last ten years, the link of systemic inflammation and cancer progression, as well as prognosis, became more and more evident. In this context, several groups were able to demonstrate that the ratio of lymphocytes and monocytes might play a meaningful role as a potential prognostic factor in various human solid cancer types. Stotz *et al.* were the first to recently report data on a cohort of more than 370 patients with stage III colon cancer.[166] They found an elevated pre-operative LMR statistically significantly being associated with increased time to recurrence and OS in multivariate analysis. Szkandera and colleagues investigated several inflammatory indices with regard to their potential prognostic relevance for predicting clinical outcomes in soft tissue sarcoma patients.[167] The authors report that a low LMR was significantly associated with decreased CSS and disease free survival in their validation cohort comprising of 170 patients. In addition, they also demonstrated to improve a frequently used prognostic nomogram by supplementing it with the LMR.[167] Finally, our own group recently demonstrated that a low LMR represented an independent prognostic factor regarding CSS in a large cohort of non-metastatic clear cell renal cell carcinoma patients.[168]

To the best of our knowledge, we are the first to report data on the potential role of the pre-operatively assessed LMR in localised UTUC patients. We found that age at the date of surgery, pathologic T-stage, as well as the pre-operative LMR were

independent predictors of patients' OS. Since all of the above (retrospective) studies investigated patients with various cancer types, using different LMR cut-off values, a direct comparison of the results is not feasible. Moreover, a definitive explanation for our findings in localised UTUC patients remains speculative. On the one hand, T lymphocytes were identified to play a significant role in anti-tumour immune reactions by several mechanisms including the ability to enhance tumour cell apoptosis.[174] Influencing T-lymphocytes by immune checkpoint blockade inhibitors (e.g. ipililumap) carries a huge therapeutic potential and is currently under clinical investigation for several tumour types. On the other hand, tumour-associated macrophages (TAM) developing from mononuclear cell lineages, have been demonstrated to being able to inhibit, as well as to facilitate cancer progression and metastatic tumour spread.[175,176] Bingle and colleagues were able to demonstrate an association between high macrophage density and poor clinical outcomes in various human cancer types, such as breast-, lung-, cervix-, prostate-, as well as urothelial carcinoma of the bladder.[177] Recently, Partecke *et al.* showed an induction of M2-macrophages by tumour cells, as well as a tumour growth promotion by M2-macrophages in pancreatic cancer tissue.[178] Taken together, this data indicate an enormous pro-tumourigenic potential of monocytes by inducing different TAM phenotypes that are able to promote cancer development and progression. The question, whether circulating monocyte levels might denote an increased production of tissue macrophages and thus might be regarded as a potential surrogate biomarker, is not answered yet. Therefore, our findings should be interpreted with great caution, since external validation of potential prognostic risk assessment tools using independent cohorts of patients is considered paramount prior to the general applicability of a prognostic marker or model.[179] Importantly, when implementing prognostic factors or therapeutic measurements, an

independent confirmation of the utility has to be confirmed for different ethnical subgroups with different genetic background.[179] Additionally, as with all retrospective studies, the limitations of our study are inherent to the design, including the retrospective data collection. Moreover, the patients from this study underwent surgical treatment by multiple surgeons. Finally, the ideal cut-off value for the pre-operative LMR in our study was 2.0. The ideal threshold for the continuously coded LMR was calculated by testing all possible thresholds that would discriminate between patients' survival and cancer-related death by Cox proportional analyses. Furthermore, an ideal and generalizable LMR threshold in UTUC has yet to be determined.

In conclusion, our data clearly indicate that an elevated pre-operative LMR might represent an independent prognostic factor for OS in non-metastatic UTUC patients and to the best of our knowledge is the first study to evaluate it's potential prognostic impact. We thus believe this parameter should be considered in future prognostic studies and might enable a better ability to predict UTUC patients' clinical outcome when integrated into established prognostic models.

13. Legends

Table 1 Descriptive clinico-pathological parameters of the study cohort comprising of patients with non-metastatic upper urinary tract urothelial carcinoma (UTUC) [n=182].

Table 2 Crosstable demonstrating the association of the lymphocyte-monocyte ratio (LMR) with various clinico-pathological parameters in the study cohort (n=182).

Table 3 Univariate and multivariate analysis of clinico-pathological parameters for the prediction of overall survival (OS) in patients with non-metastatic upper tract urothelial carcinoma (UTUC) [n=182].

Fig. 1 Kaplan-Meier curves predicting overall survival (OS), groups categorized by the pre-operative lymphocyte-monocyte ratio (LMR).

14. Table 1 Descriptive clinico-pathological parameters of the study cohort comprising of patients with non-metastatic upper urinary tract urothelial carcinoma (UTUC) [n=182].

Parameter	No. (%)
Age at operation (yrs.)	
mean ± SD	69.0 ± 10.3
median	70.0
interquartile range	62.7-77.2
<65	58 (31.9)
≥65	124 (68.1)
Gender	
Male ♂	111 (61.0)
Female ♀	71 (39.0)
Tumour site	
left	97 (53.3)
right	85 (46.7)
Tumour location	
Ureter	82 (45.1)
Pelvis	100 (54.9)
pathologic T-stage	
pT-1	83 (45.6)
pT-2-4	99 (54.4)
Tumour grade	
G-1 + G-2	99 (54.4)
G-3 + G-4	83 (45.6)
Presence of histologic tumour necrosis	
no	158 (86.8)
yes	24 (13.2)
Monocytes	
mean ± SD	0.67 ± 0.32
median	0.60
range	0.20-3.00
Lymphocytes	
mean ± SD	1.48 ± 0.59
median	1.40
range	0.10-4.10
Lymphocyte-monocyte ratio (LMR)	
mean ± SD	1.76 ± 0.43
median	2.00
range	0.23-24.00
< 2.0	43 (23.6)
≥ 2.0	139 (76.4)

Legend
SD: standard deviation

Table 2 Crosstable demonstrating the association of the lymphocyte-monocyte ratio (LMR) with various clinico-pathological parameters in the study cohort (n=182).

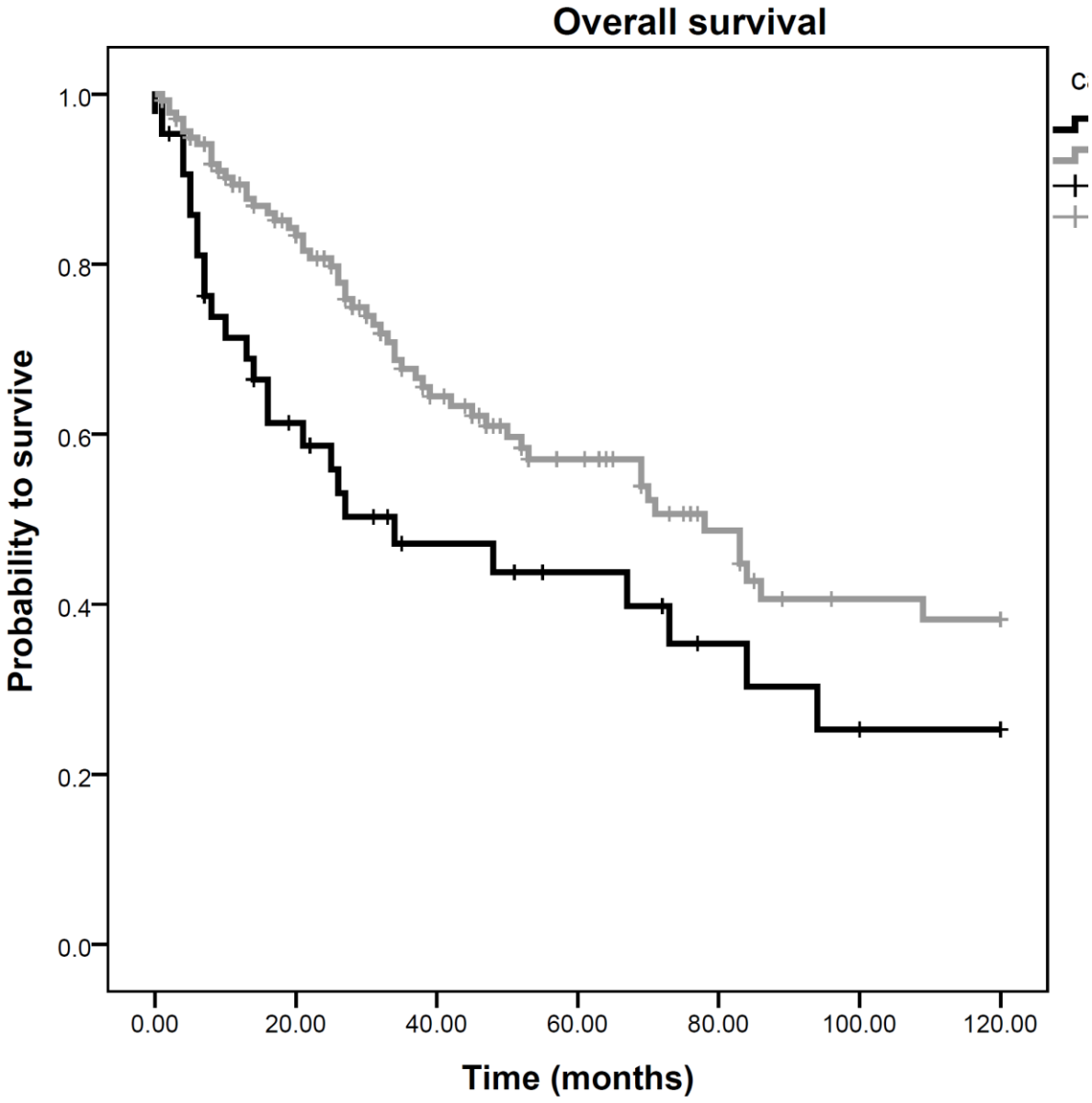
Parameter	Lymphocyte-monocyte ratio (LMR)		Total	*p*-value
	< 2.0	**≥ 2.0**		
Age at operation (yrs.)				
< 65	10 (23.3%)	48 (34.5%)	58 (31.9%)	
≥ 65	33 (76.7%)	91 (65.5%)	124 (68.1%)	0.165
Gender				
Male ♂	22 (51.2%)	89 (64.0%)	111 (61.0%)	
Female ♀	21 (48.8%)	50 (36.0%)	71 (39.0%)	0.131
Tumour site				
left	20 (46.5%)	77 (55.4%)	97 (53.3%)	
right	23 (53.5%)	62 (44.6%)	85 (46.7%)	0.308
Tumour location				
Ureter	18 (41.9%)	64 (46.0%)	82 (45.1%)	
Pelvis	25 (58.1%)	75 (54.0%)	100 (54.9%)	0.630
pathologic T-stage				
pT-1	16 (37.2%)	67 (48.2%)	83 (45.6%)	
pT-2-4	27 (62.8%)	72 (51.8%)	99 (54.4%)	0.206
Tumour grade				
G-1 + G-2	24 (55.8%)	75 (54.0%)	99 (54.4%)	
G-3 + G-4	19 (44.2%)	64 (46.0%)	83 (45.6%)	0.831
histologic tumour necrosis				
no	37 (86.0%)	121 (87.1%)	158 (86.8%)	
yes	6 (14.0%)	18 (12.9%)	24 (13.2%)	0.865

Table 3 Univariate and multivariate analysis of clinico-pathological parameters for the prediction of overall survival (OS) in patients with non-metastatic upper tract urothelial carcinoma (UTUC) [n=182].

Parameter	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age at operation (yrs.)				
< 65	1 (reference)	0.005	1 (reference)	0.008
≥ 65	2.169 (1.271-3.701)		2.104 (1.216-3.641)	
Gender				
Female ♀	1 (reference)	0.608	1 (reference)	0.062
Male ♂	1.124 (0.719-1.757)		1.574 (0.977-2.536)	
Tumour site				
left	1 (reference)	0.142	1 (reference)	0.254
right	1.385 (0.897-2.138)		1.293 (0.831-2.010)	
Tumour location				
Ureter	1 (reference)	0.040	1 (reference)	0.105
Pelvis	1.603 (1.022-2.514)		1.496 (0.919-2.437)	
pathologic T-stage				
pT-1	1 (reference)	<0.001	1 (reference)	0.005
pT-2-4	2.999 (1.849-4.864)		2.148 (1.257-3.670)	
Tumour grade				
G-1+G-2	1 (reference)	<0.001	1 (reference)	0.058
G-3+G-4	2.427 (1.561-3.772)		1.620 (0.985-2.664)	
Presence of histologic tumour necrosis				
no	1 (reference)	<0.001	1 (reference)	0.245
yes	2.918 (1.688-5.046)		1.453 (0.774-2.729)	
Lymphocyte-monocyte ratio (LMR)				
< 2.0	1 (reference)	0.020	1 (reference)	0.021
≥ 2.0	0.574 (0.361-0.915)		0.562 (0.345-0.915)	

Legend
HR: hazard ratio

15. Fig. 1 Kaplan-Meier curves predicting overall survival (OS), groups categorised by the pre-operative lymphocyte-monocyte ratio (LMR).



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