Title Page

The impact of cisplatin or non-cisplatin containing chemotherapy on long-term and conditional survival of patients with advanced urinary tract cancer.

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Conflict of Interest

"The authors declare no potential conflicts of interest"

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Abstract

Purpose: The impact of cisplatin utilization on long-term survival of unselected patients with advanced urinary tract cancer (aUTC) has not been adequately investigated. We used a multinational database to study long-term survival and the impact of treatment type in unselected aUTC patients.

Materials and Methods: 1333 patients with aUTC (cT4bN0M0, cTanyN+M0, cTanyNanyM+), transitional-cell, squamous or adenocarcinoma histology who received systemic chemotherapy and had available survival data were selected. Long-term survival was defined as alive at 3 years following initiation of 1st-line chemotherapy. Conditional overall survival (COS) analysis was employed to study change in prognosis given time survived from initiation of 1st-line chemotherapy.

Results: Median follow-up was 31.7 months. The combination of cisplatin utilization and cisplatin eligibility accurately predicted long-term survival. Eligible patients treated with cisplatin conferred a 31.6% probability of 3-year survival (95% confidence interval [CI]: 25.1-38.3), while 2-year COS for patients surviving 3-years after initiation of cisplatin-based chemotherapy was 83% (95% CI: 59.7-93.5). The respective probabilities for patients who were ineligible-for-cisplatin or not treated with cisplatin despite eligibility were 14% (95% CI: 10.8-17.6) and 49.3% (95% CI: 28.2-67.4). 2-year COS remained significantly different between these two groups up to 3 years after chemotherapy initiation.

Conclusions: Cisplatin-based therapy was associated with the highest likelihood of long-term survival in patients with aUTC and should be utilized in patients who fulfill the established eligibility criteria.

Impact: Eligible-for-cisplatin patients with aUTC treated with cisplatin-based combination chemotherapy have a 26% chance of 5-year survival. Therefore, deviations from eligibility criteria should be avoided in everyday practice.

Introduction

Cisplatin-based chemotherapy is the treatment of choice in advanced urinary tract cancer (aUTC). Although most patients progress and die due to their disease, long-term, disease-free survival has been reported in 15-20% of patients receiving this treatment [1-3]. The ability to predict improved outcomes has been enhanced by established algorithms [4] that delineate different prognostic groups among aUTC patients [5,6]. It should be emphasized, however, that long-term survival data was derived primarily from clinical trials, while data pertaining to outcomes in the real-word setting is lacking. More importantly, a significant proportion of patients with aUTC do not receive cisplatin-based chemotherapy [7] mainly due to concerns of increased toxicity and/or limited efficacy in certain patient groups. In addition, 25% of patients do not receive cisplatin-based chemotherapy in everyday practice despite eligibility [8,9] according to recently established criteria [10].

Despite platinum-based combination chemotherapy representing the standard treatment for aUTC for decades, several fundamental "real world" clinical questions remain unanswered. For example, the probability of long-term survival for aUTC patients not receiving cisplatin-based chemotherapy is not well described. Furthermore, whether use of non-cisplatin-based regimens compromises the chance for long term survival in patients otherwise eligible is not known. These questions are particularly germane in the context of the growing enthusiasm surrounding durable disease control with immune checkpoint blockade as such findings have the potential to rapidly overshadow the critical role of cisplatin-based chemotherapy in a subset of patients and lead to "indication-drift" despite first-line approvals currently limited to the cisplatin-ineligible population [11,12]. Finally, whether the prognostic impact of baseline variables and differences in treatment lessen based on the duration of post-

treatment survival, a concept known as conditional survival [13-15], has not been well studied.

The Retrospective International Study of Cancers of the Urothelium (RISC) database represents the largest multi-national database of urinary tract cancer patients worldwide [8,16-18]. It includes patients regardless of their participation in clinical trials, treated at the United States, Europe, Israel and Canadaduring the last decade. It, thus, ensures an adequately long follow up and wide representation of global contemporary trends in the utilization of chemotherapy for the treatment of aUTC, since it predates the approval of novel immunotherapies. Using this database we recently showed the importance of applying eligibility-for-cisplatin criteria in order to select patients who derive maximum benefit from cisplatin-based chemotherapy [8]. We used this database to study long-term survival among patients with aUTC treated with chemotherapy and to evaluate the importance of cisplatin utilization in this context.

Materials and Methods

Patients

The RISC database includes data of patients with localized muscle-invasive or advanced UTC (defined as primary carcinoma of the urinary bladder, renal pelvis, ureter or urethra). Data collection and quality control have been previously described [8,16]. The study was approved by the ethics committees at each participating institution. The database was locked in October 2015.

For the current study, patients with advanced disease (defined as metastatic disease or non metastatic inoperable disease, i.e. clinical stages T4bN0M0, TanyN+M0 and TanyNanyM+) and who received at least one line of systemic chemotherapy were

selected. Eligible histologies were: pure or mixed urothelial carcinoma, pure squamous and pure adenocarcinoma. Patients were excluded if they a. did not fulfil the criteria of advanced disease; b. had insufficient information regarding the extent of disease, survival data or chemotherapy details; c. had non-eligible histologies (e.g. pure or mixed small-cell). Administration of chemotherapy for radiosensitization purposes only was not considered eligible as systemic treatment.

Statistical analysis

The primary end points of our analyses were: probability of long-term survival, defined as survival beyond 3 years from the time of initiation of 1st-line chemotherapy for aUTC and 2-year conditional overall survival (COS). The latter was defined as the probability of surviving an additional 2 years at a given time point since the initiation of 1st-line chemotherapy. We also planned key secondary analyses to assess the association of long-term survival and COS with type of chemotherapy used in 1st-line (cisplatin vs. non-cisplatin) and eligibility-for-cisplatin. Details of the statistical methodology are included in the Supplementary Material.

Results

Patients

The flow chart of our analyses is depicted in Figure 1. From the 3024 patients of the RISC database, 1333 with advanced UTC, managed at 29 centers between 2000 and 2013, fulfilled selection criteria. Their baseline characteristics and detailed description of chemotherapy administered have been previously published [8].Cisplatin-based 1st-line chemotherapy was administered to 669 patients, carboplatin-based to 399 and other therapies to 265. Patients receiving carboplatin-based or non-cisplatin/non-

carboplatin-based 1st-line chemotherapy were grouped together, since no significant OS differences were observed between these two groups in our previous study [8]. Selected baseline characteristics as well as response rates to 1st-line chemotherapy according to this categorization are shown in Supplementary Tables S1 and S2. Median follow up for the 1333 patients was 31.7 months (95% CI: 29.2-35.3). During this follow-up, 872 died (disease: 782, toxicity: 9, other causes: 24, unknown reason: 57).

Adequate data to assess eligibility-for-cisplatin were available for 929 patients: 429 patients (46%) had at least one criterion for ineligibility. One hundred-twenty-four patients (26%) who did not receive cisplatin were eligible for this agent.

Long-term and conditional survival analyses

Cisplatin-based therapy and lower risk according the MSKCC stratification have been independently associated with improved survival in this population [8] (Supplementary Fig. S1). 3, 4 and 5-year survival rates were also higher within these groups (Table 1). We have also reported that the interaction between eligibility-for-cisplatin and cisplatin utilization was significant in a multivariate cox regression model applied to this population [8]. This interaction is also supported by the current analyses: the difference in the probability of long-term survival was more pronounced when cisplatin utilization was stratified according to eligibility-for-cisplatin (Table 1). The probability of eligible patients treated with cisplatin being alive at 3 and 5 years after initiation of 1st-line chemotherapy were 31.6% (95% CI: 25.1-38.3) and 26.2% (95% CI: 19.1-33.8), respectively. This is in contrast to the long-term outcome of eligible patients not treated with cisplatin-based chemotherapy: their 3-year probability of survival was only 12.8% (95% CI: 6.5-21.1) and no patient of this

group survived 5 years (Table 1). Since our previous data showed an association of non-cisplatin use among eligible patients with higher risk according to the MSKCC algorithm [8], we investigated the impact of not utilizing cisplatin despite eligibility on long-term survival within the low and intermediate MSKCC risk groups of eligible-for-cisplatin patients (no eligible patients belonged to high-risk group). Cisplatin utilization conferred a long-term survival advantage irrespective of MSKCC risk category (Table 2, Supplementary Fig. S2), although this analysis is limited by the small number of patients in each subgroup. Probability of 5-year survival was below 10% among ineligible-for-cisplatin patients, regardless of the platinum analogue used. Since no significant long-term survival differences between ineligible and eligible/non-cisplatin treated patients were observed (Table 1), we grouped these patients for further analyses.

Table 1 shows the 2-year COS over time from 1st-line chemotherapy initiation. There was a reduction in the risk of death (Figure 2) and an increase in 2-year COS with time in all groups studied (Table 1, Figure 3). Interestingly, this probability converged (in terms of magnitude and statistical significance) in the groups defined by MSKCC risk and therapy at 18 and 30 months, respectively (Table 1, Figure 3). In contrast, this phenomenon was not observed when treatment effect was tabulated according to cisplatin eligibility (Table 1, Figure 3): treatment with cisplatin continued to confer significantly higher probability of long-term survival to eligible patients up to the 3-year landmark analysis: cisplatin-treated eligible patients who were alive at 3 years had an 83% (95% CI: 59.7-93.5) chance of surviving 2 more years as opposed to 49.3% (95% CI: 28.2-67.4) for the remaining population (p=0.034).

Characterization of long-term survival

For this analysis alive patients with a follow up shorter than 3 years were excluded. Therefore, 954 patients (71.6% of the total) (Table 3 and Supplementary Table S3) were analyzed. Long-term survival (n=128) was associated with better renal function, lower frequency of bone (18% vs. 29.4%, p=0.007), liver (8.6% vs. 21.2%, p=0.001) and distant metastases (43.8% vs. 63%, p<0.001), better PS (PS 0 54.3% vs. 26.6%, p<0.001), low risk according to the MSKCC risk stratification (54.3% vs. 30.6%, p<0.001), use of cisplatin-based chemotherapy (65.6% vs. 45.2%, p<0.001) and higher response rate to 1st-line chemotherapy (58.8% vs. 29.9%, p<0.001).

To address a frequent clinical question of the efficacy of consolidative surgery, we studied the association of this strategy with long-term survival. Sixty-eight patients underwent consolidative surgery following 1st-line chemotherapy (Supplementary Table S1). Patients who underwent surgery had a higher chance of long-term survival (16 [14%] vs. 27 [3.6%], p<0.001). Detailed descriptions of surgery performed and the outcomes following surgery are shown in Supplementary Table S4. Long-term survivors had surgery after at least stabilization of their disease in all but one case, in contrast to patients not surviving 3 years who had surgery after progression on chemotherapy in 10 cases. Surgery among patients surviving at least 3 years after the initiation of 1st-line chemotherapy more frequently included all known disease sites (93% vs. 23%, p<0.001) and was associated with pathological (pCR) (50% vs. 18%, p=0.033) and radiological complete remission (RCR) (78% vs. 24%, p<0.001), compared to patients who did not survive 3 years. Eight of the 16 long-term survivors who underwent surgery have been disease-free 15-173 months following consolidation surgery.

Discussion

To our knowledge, this retrospective series is the first to demonstrate that long-term survival is achievable in patients with aUTC, in a real-world, multi-national setting, especially when cisplatin is utilized in eligible patients. Similar to COS analyses in other solid tumors, we found that the probability of long-term survival is dynamic and increased with time survived after the initiation of chemotherapy. These findings are important for optimizing treatment decisions and counselling patients in everyday practice and also useful in the context of the changing treatment paradigm in this disease. Type of chemotherapy decisively affected the chances of patients with aUTC to experience long-term survival. The use of cisplatin-based chemotherapy in patients who were eligible, according to the criteria of Galsky et al, was associated with a 31.6% chance of being alive at 3 years and a 26.2% chance of being alive at 5 years. Furthermore, being alive at 3 years conferred an 83% probability of being alive at 5 years. Whether this probability indicates cure from the disease or (partially at least) represents imbalances in 2nd-line treatment, cannot be answered by our study but it underscores the need for further research into the characterization and outcome of long-term survivors with aUTC. Eligible patients not treated with cisplatin-based chemotherapy had a significantly lower probability of long-term survival, which was similar to that of ineligible patients. In addition, apart from the well-established factors of PS and site of metastases, response to chemotherapy was shown to be an important predictor of long-term survival. Specifically, CR was reported in 23.5% of patients living for at least 3 years, in contrast, to only 3.9% among patients not reaching this time. Both these findings emphasize the importance of optimization of cisplatin use in patients with aUTC.

We found that eligibility-for-cisplatin may be a more reliable predictor of long-term survival than the MSKCC risk stratification, especially as the time from initiation of chemotherapy increases: the difference in the probability of long-term survival among the different MSKCC groups weakened with time, while the difference between cisplatin-treated/eligible and the remaining patients persisted up to 3 years. Although this study was not aimed to formally compare the two prognostic models, our analyses suggest that the combination of eligibility-for-cisplatin and cisplatin utilization has comparable prognostic value to the long established MSKCC risk stratification. This is not surprising, if we consider that eligibility criteria include one of the two factors used in the MSKCC model, namely ECOG PS.

Long-term survival is achievable following non-cisplatin-based chemotherapy but to a significantly lower extent than in cisplatin-treated counterparts. This population is clearly in need of novel therapies. The emergence of modern immunotherapy targeting the interaction between the programmed death (PD)-1 receptor on tumor T-lymphocytes and its ligand PD-L1 has set new standards in 1st and 2nd-line treatment of aUTC [10,11,19,20]. Data from recent studies suggest that long-lasting disease control can be obtained with these agents albeit in a minority of patients. Since these agents are compared to or studied with chemotherapy, the benchmarks of the long-term efficacy of chemotherapy provided here could be particularly relevant. For example, a 3-year OS rate of 27% (95% CI, 17%-36%) was reported for patients treated with atezolizumab in a phase I study [21]. This compares favorably with the respective rate of 22% reported in this study, especially when we take into consideration that the patients who received atezolizumab had been heavily pre-treated. The majority of those patients were also cisplatin-ineligible, which would lower the 3-year OS rate in our population to 15%. Recognizing these are indirect

comparisons, they highlight the promise of these novel and generally more tolerable agents.

Our work also supports the potential efficacy of consolidation surgery. Long-term survival was achieved only in 1 of 11 cases (9%), when surgery was performed after progression on chemotherapy, as opposed to 8 of the 21 patients (38%) who were operated following an objective response to chemotherapy. Resection of all sites of known disease seems to be necessary to achieve long-term survival. Type of chemotherapy did not seem to affect post-surgery outcome and while pCR and/or clinical CR following surgery were predictive, they were not always necessary for long-term survival, especially when all disease sites had been removed. These analyses are limited by the small number of patients, but they may offer the theoretical basis for future research into the selection of patients likely to benefit from surgery after a response to platinum-based chemotherapy.

Our study has certain limitations associated with its retrospective nature. Inaccuracies in reporting may have occurred in spite of the quality control of the data, which was carried out. Selection biases are also inherent to retrospective analyses. Although we cannot completely exclude this possibility, the fact that the value of the MSKCC risk stratification was confirmed by our analyses indicates that the RISC population is adequately representative of everyday practice.

Our data are potentially useful for clinical practice and future research. They demonstrate the heterogeneity in the behavior of aUTC, resulting in prognostically distinct populations. Hopefully, the new discoveries in the molecular characterization of urothelial cancer and the study of molecular markers will lead to an era of individualized management [22]. Until then, offering cisplatin to those eligible seems

to be the most effective tool to optimally utilize cisplatin-based chemotherapy and achieve long-term survival in a sizable proportion of patients. Additionally, our work underscores the importance of a multidisciplinary approach to aUTC with consideration of consolidative surgery with resection of all known disease sites, when feasible, following favorable response to 1st-line chemotherapy. Finally, we provide useful clinical benchmarks of the outcome of the various subgroups of patients with aUTC, which could be used for the design of future trials of novel agents in this disease and in ongoing prognosis discussions at the bedside.

Acknowledgement

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Figure legends

Figure 1. Study flow chart

Figure 2. Change of hazard of death over time in 1333 patients treated with 1st-line chemotherapy for advanced urinary tract cancer according to: (a) Memorial Sloan Kettering Cancer Center risk model, (b) Utilization of cisplatin-based chemotherapy unstratified and stratified according to eligibility-for-cisplatin.

Figure 3. Two-year conditional overall survival over time, stratified by (a) Memorial Sloan Kettering Cancer Center risk model and by (b) the combined effect of eligibility-for-cisplatin and cisplatin utilization. Lines connecting the conditional overall survival at each time point do not represent a curve based on a model but are simply linear connectors between estimates. The x-axis values are identical for each time point for the two groups compared, and the figures are staggered for visual effect. «Other» denotes cisplatin-ineligible patients and eligible patients not treated with cisplatin.

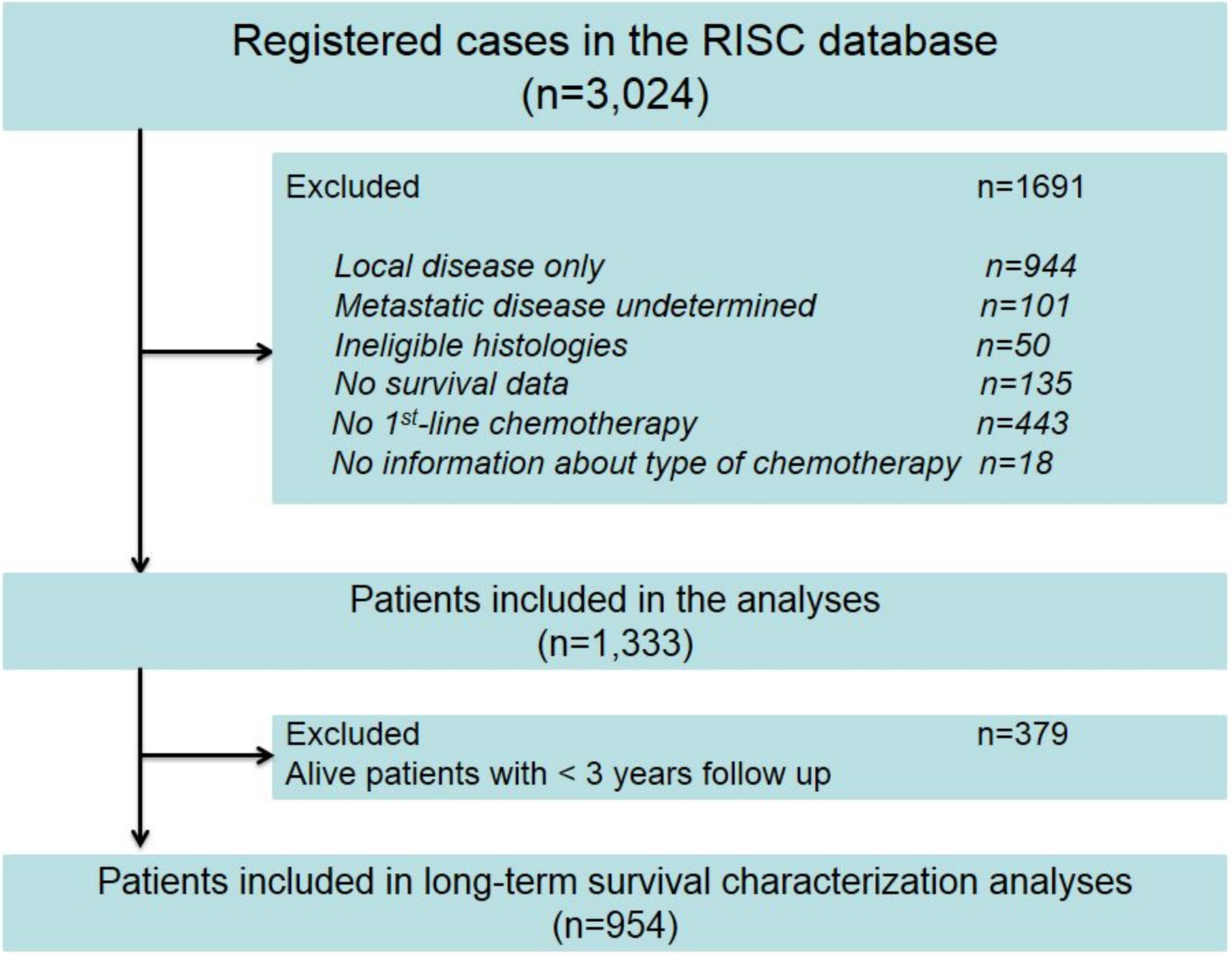
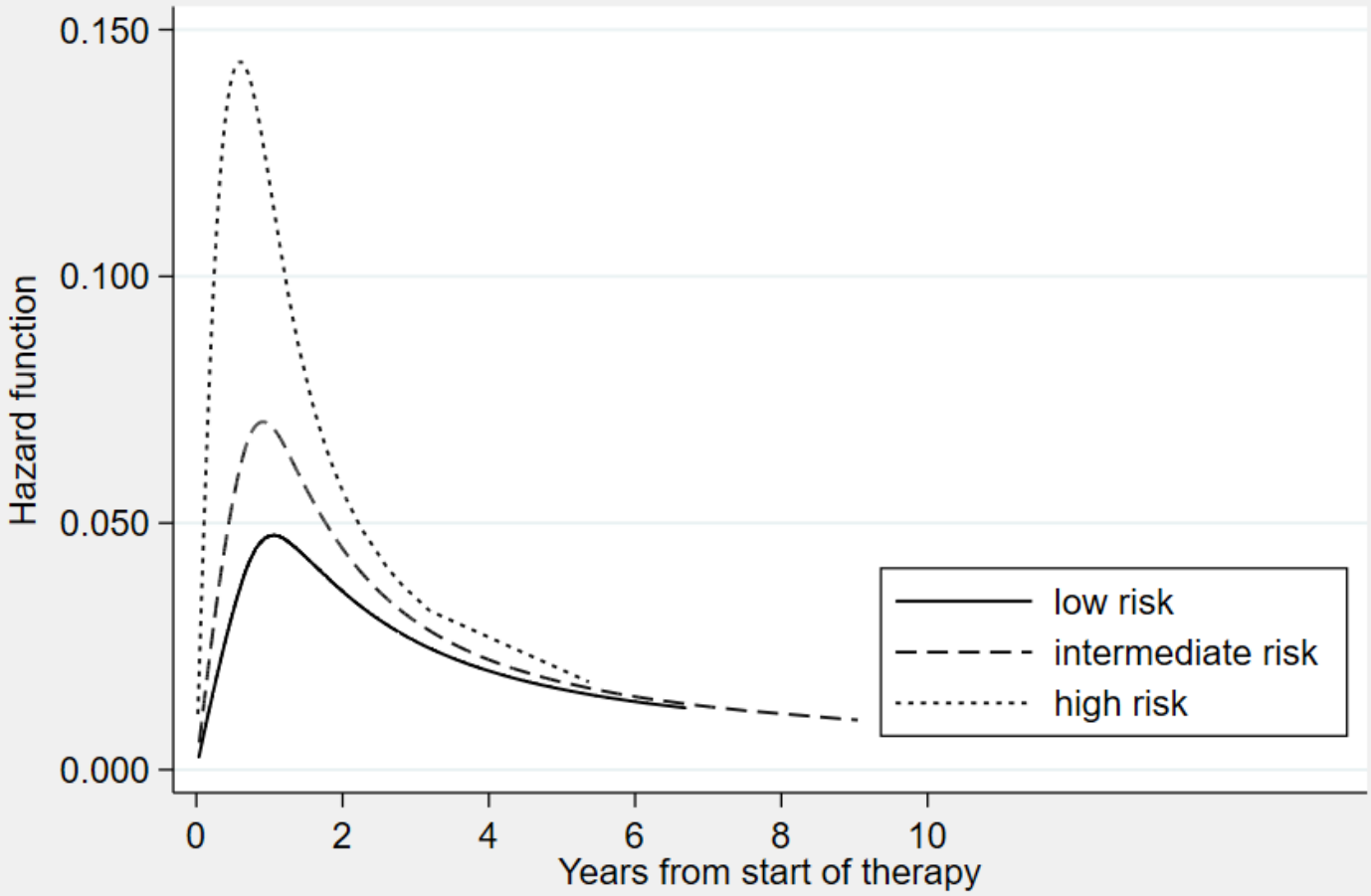
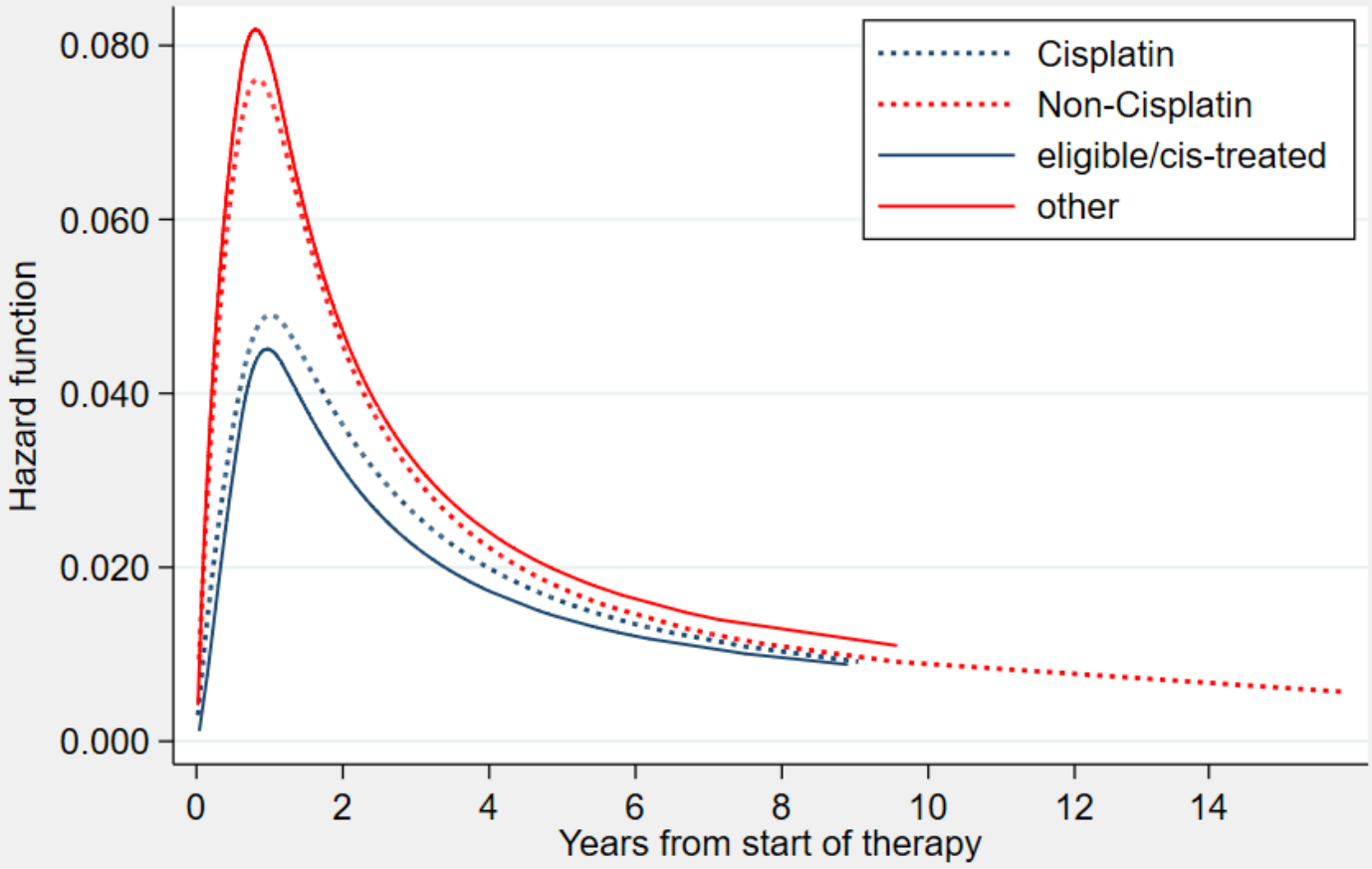

Registered cases in the RISC database
(n=3,024)
Excluded n=1691
Local disease only n=944
Metastatic disease undetermined n=101
Ineligible histologies n=50
No survival data n=135
No 1st-line chemotherapy n=443
No information about type of chemotherapy n=18
Patients included in the analyses
(n=1,333)
Excluded n=379
Alive patients with < 3 years follow up
Patients included in long-term survival characterization analyses
(n=954)

fig 2A



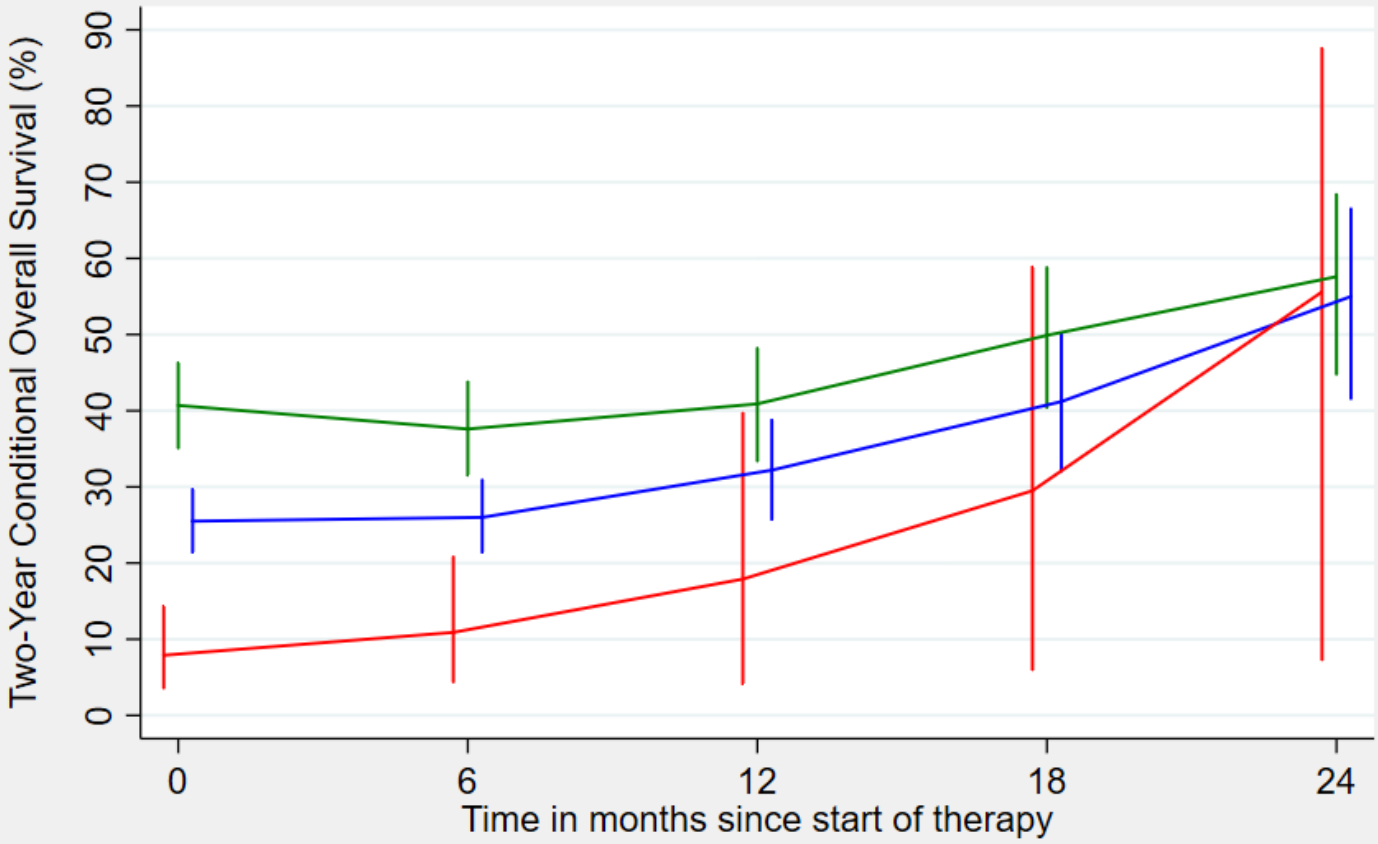
Flexible parametric model on the log cumulative odds scale

fig 2B



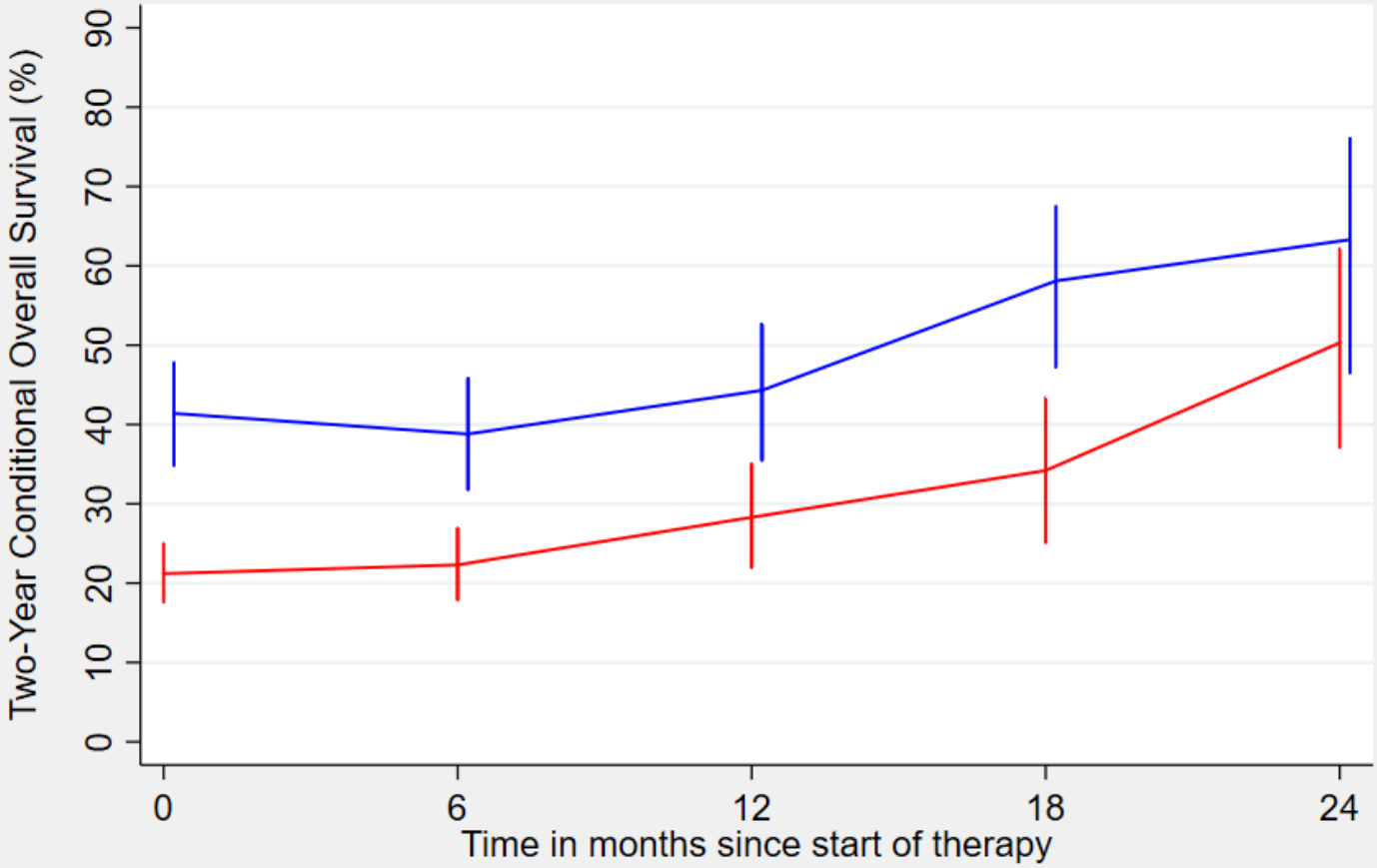
Flexible parametric model on the log cumulative odds scale for therapy groups & on the probit scale for the cis/fit groups

fig 3A



green: low risk
blue: intermediate risk
red: high risk

fig 3B



blue: eligible/cis-treated
red: other

Table 1. Probability of 3-, 4- and 5-year survival and 2-year Conditional survival of 1333 patients with advanced urinary tract cancer treated with 1st-line chemotherapy

	Probability of surviving (years) (95% CI)			
	3	4	5	P*
Total	22.2 (19.5-25.1)	17.3 (14.6-20.2)	13.5 (10.8-16.6)	
Therapy group				<0.001
Cisplatin (n=669)	29.3 (25.1-33.6)	22(17.7-26.5)	19.4 (15.1-24.3)	
Non-cisplatin (n=664)	15.1 (11.8-18.8)	12.4 (9.3-16)	8 (5.1-11.7)	
MSKCC risk				<0.001
Low (n=366)	29.1 (23.6-34.9)	23.4 (17.9-29.5)	18.1 (12-25.2)	
Intermediate (n=551)	18 (14.3-22.1)	14 (10.4-18.2)	10.7 (7.1-15)	
High (n=131)	4.4 (1.1-11.2)	4.4 (1.1-11.2)	4.4 (1.1-11.2)	
Eligible-for-cisplatin				<0.001
Yes (n=399)	25.9 (20.8-31.2)	20.7 (15.3-26.6)	18.1 (12.5-24.5)	
No (n=530)	14.2 (10.7-18.3)	11.3 (7.9-15.3)	8.2 (4.9-12.5)	
Cisplatin eligibility & Cisplatin utilization				<0.001
Cisplatin-eligible/Received Cisplatin (n=275)	31.6 (25.1-38.3)	26.2 (19.1-33.8)	26.2 (19.1-33.8)	
Cisplatin-eligible/Did not receive cisplatin (n=124)	12.8 (6.5-21.1)	7.7 (2.5-16.6)	-	
Cisplatin-ineligible/Received Cisplatin (n=176)	16.9 (10.2-25)	9.9 (4.4-18)	9.9 (4.4-18)	
Cisplatin-ineligible/Did not receive cisplatin (n=354)	13 (9-17.7)	11.6 (7.8-16.4)	7.5 (4-12.6)	
Cisplatin-eligible AND treated with cisplatin (n=275)	31.6 (25.1-38.3)	26.2 (19.1-33.8)	26.2 (19.1-33.8)	<0.001
Other# (n=654)	14 (10.8-17.6)	10.7 (7.7-14.2)	6.9 (4.1-10.7)	

2-year Conditional survival

Time from initiation of 1st-line chemotherapy	Total	Cisplatin			MSKCC group				Therapy group		
		Yes	No	p	Low	Intermediate	High	p	EfC/Cisplatin	Other#	P*
0 mos (n=1333)	31.4 (28.5-34.3)	37.7 (33.5-41.9)	24.9 (21.1-28.8)	<0.001	40.7 (35.1-46.3)	25.5 (21.4-29.7)	7.9 (3.6-14.4)	<0.001	41.4 (34.8-47.8)	21.2 (17.6-25)	<0.001
6 mos (n=1024)	31.9 (28.6-35.2)	37.7 (33.1-42.4)	24.9 (20.5-29.6)	<0.001	37.6 (31.5-43.8)	26 (21.4-30.9)	10.9 (4.4-20.8)	<0.001	38.8 (31.8-45.8)	22.3 (17.9-26.9)	<0.001
12 mos (n=644)	37.5 (33.2-41.9)	43.3 (37.5-49)	29.7 (23.5-36.1)	0.010	40.9 (33.4-48.2)	32.2 (25.7-38.8)	17.9 (4.1-39.7)	0.019	44.3 (35.5-52.7)	28.3 (22-35)	<0.001
18 mos (n=397)	45.2 (39.4-50.9)	51.3 (43.5-58.9)	36.7 (28-45.3)	0.023	49.9 (40.4-58.8)	41.2 (32.1-50.1)	29.5 (6-58.9)	0.146	58.1 (47.2-67.5)	34.2 (25.1-43.4)	0.004
24 mos (n=259)	55 (47.4-62)	58.3 (47.8-67.3)	49.7 (38.1-60.3)	0.041	57.6 (44.8-68.4)	55 (41.6-66.5)	55.6 (7.3-87.6)	0.920	63.3 (46.5-76.1)	50.3 (37.1-62.2)	0.022
30 mos (n=186)	56.4 (47-64.9)	60.3 (48.2-70.5)	50.8 (35.7-64.1)	0.353	63.2 (47.5-75.4)	50.1 (33.5-64.7)	66.7 (5.4-94.5)	0.930	74.1 (54.1-86.3)	45 (28.4-60.3)	0.018
36 mos (n=128)	60.8 (49.4-70.4)	66.4 (52.5-77)	53 (33.7-69.1)	0.872	62.2 (40.1-78.2)	59.3 (39.7-74.3)	100	0.739	83 (59.7-93.5)	49.3 (28.2-67.4)	0.034

OS: overall survival; HR: hazard ratio; CI: confidence interval; MSKCC: Memorial Sloan Kettering Cancer Center;EfC: eligible-for-cisplatin; #: EfC not treated with cisplatin and ineligible patients irrespective of type of chemohterapy; * p-value of log-rank test

Table 2. Impact of cisplatin utilization on eligible-for-cisplatin patients according to Memorial Sloan Kettering Cancer Center risk group. No poor-risk patients were treated with cisplatin

MSKCC risk	Probability of surviving (years) (95% CI)			p
	3	4	5	
Low				<0.001
Cisplatin (n=128)	39.3 (29.1-49.3)	31.4 (20.5-43)	31.4 (20.5-43)	
Non-cisplatin (n=41)	-	-	-	
Intermediate				0.021
Cisplatin (n=147)	25 (17.1-33.7)	22.2 (13.9-31.8)	22.2 (13.9-31.8)	
Non-cisplatin (n=83)	16.7 (8.6-27.1)	10 (3.3-21.3)	-	

MSKCC: Memorial Sloan Kettering Cancer Center; CI: confidence interval

Table 3. Baseline characteristics associated with survival ≥ 3 years among 954 patients with advanced urinary tract cancer treated with first-line chemotherapy

Characteristic	**Total** (n=954)	**dead at 3 years** (n=826)	**alive at ≥3 years** (n=128)	*P*[1]
Age(median, range)*	67.3 (34-92.9)	67.7 (34-92.9)	66.6 (34.9-86.1)	0.034
Creatinine clearance(median, range)*	62.6 (9.1-334.6)	62.1 (9.1-334.6)	73.5 (25.6-198.6)	0.005
		n (%)		
Gender*				0.749
M	746 (78.6)	644 (78.4)	102 (79.7)	
F	203 (21.4)	177 (21.6)	26 (20.3)	
Histology*				0.961
Transitional	832 (88.1)	720 (88.1)	112 (88.2)	
Mixed	71 (7.5)	61 (7.5)	10 (7.9)	
Other	41 (4.3)	36 (4.4)	5 (3.9)	
Metastatic sites				
Locoregional	190 (19.9)	169 (20.5)	21 (16.4)	0.285
Lymph nodes	600 (62.9)	511 (61.9)	89 (69.5)	0.095
Bone	266 (27.9)	243 (29.4)	23 (18)	0.007
Lung	261 (27.4)	231 (28)	30 (23.4)	0.285
Liver	186 (19.5)	175 (21.2)	11 (8.6)	0.001
Brain	21 (2.2)	15 (1.8)	6 (4.7)	0.039
Adrenal	26 (2.7)	24 (2.9)	2 (1.6)	0.385
Peritoneum	37 (3.9)	31 (3.8)	6 (4.7)	0.610
Distant**	576 (60.4)	520 (63)	56 (43.8)	<0.001
Post chemotherapy surgery*				<0.001
Yes	43 (5)	27 (3.6)	16 (14)	
No	821 (95)	723 (96.4)	98 (86)	
Primary site *				0.314
Bladder	760 (81.2)	661 (81.7)	99 (78)	
Other	176 (18.8)	148 (18.3)	28 (22)	
ECOG PS *				<0.001
0	234 (30)	183 (26.6)	51 (54.3)	
1	397 (50.8)	358 (52.1)	39 (41.5)	
2	124 (15.8)	122 (17.8)	2 (2.1)	

3	24 (3.1)	22 (3.2)	2 (2.1)	
4	2 (0.3)	2 (0.3)	0 (0)	
Risk stratification *#				<0.001
Low	261 (33.4)	210 (30.6)	51 (54.3)	
Intermediate	412 (52.8)	371 (54)	41 (43.6)	
High	108 (13.8)	106 (15.4)	2 (2.1)	
Therapy				<0.001
Cisplatin	457 (47.9)	373 (45.2)	84 (65.6)	
Non-Cisplatin	497 (52.1)	453 (54.8)	44 (34.4)	
Response to 1st line therapy				<0.001
Complete	58 (6.6)	30 (3.9)	28 (23.5)	
Partial	240 (27.2)	198 (26)	42 (35.3)	
Stable disease	203 (23)	176 (23.1)	27 (22.7)	
Progressive disease	271 (30.8)	261 (34.3)	10 (8.4)	
Non-evaluable	109 (12.4)	97 (12.7)	12 (10.1)	

1: p values for comparison of the two subgroups; SD: standard deviation; * missing values apply and are listed in Table S4; **Distant metastases: metastases outside primary site and lymph nodes; # Risk stratification according to Bajorin et al [ref 4]