Urothelial Cell Carcinoma

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chapter 2

High risk bladder cancer: current management and survival

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Abstract

Objective

To evaluate the actual pattern of care in patients with newly diagnosed high risk non muscle invasive bladder cancer (NMIBC) in the Comprehensive Cancer Center North-Netherlands (CCCN) and to assess factors associated with the choice of treatment, recurrence and progression free survival rates.

Patients and methods

Collected data of a total of 412 patients on diagnosis, staging, and treatment was evaluated to assess factors which could explain differences in choices of treatment and differences in 5 year recurrence free and progression free survival.

Results

18% of the 412 patients with high risk NMIBC underwent a trans urethral resection (TUR) as single treatment. In teaching hospitals 90.7% of the patients received adjuvant treatment after the TUR compared to 71.8 % in patients treated in non-teaching hospitals ($p<0.001$). In multivariate analysis, older age (61-74 years OR 0.40 (0.15-1.11) and 75 and older OR 0.22 (0.08-0.59); $p=0.004$) and treatment in non-teaching hospitals (OR 3.61; $p<0.001$) were associated with less adjuvant treatment after TUR. Two third of the BCG failures were still non-muscle invasive tumors (53/76). Tumor progression occurred in 84 of the 392 patients (21.4%). The mean 5-years progression free survival was 71.6% (95% CI 65.5-76.8).

Conclusion

In this pattern of care study in high risk NMIBC, older age and treatment in non-teaching hospitals were associated with less adjuvant treatment after TUR. Differences in treatment did not significantly affect 5 year recurrence free and progression free survival rates.

2 High risk bladder cancer: current management and survival

Introduction

Bladder cancer is the second most common urological cancer. Non muscle invasive forms include carcinoma in situ (CIS) and Ta/T1 carcinomas and accounts for more than half of the incidence. These tumors frequently recur, particularly in multi focal disease. Progression to muscle invasive disease is related to risk groups. The high risk group consists of patients with a high grade tumor (Grade 3) with/ without concurrent CIS or CIS alone. Progression rates in this group of patients show a wide range (12 – 52%).[1–3] Adjuvant intravesical chemotherapy, either single immediate or serial additional instillations, is effective in decreasing local recurrence in low grade tumors.[4,5] However, these instillations do not prevent progression. In high grade tumors Bacille Calmette Guérin (BCG) instillations are superior to intravesical chemotherapy to prevent or delay progression. For optimal efficacy BCG maintenance therapy is necessary.[1,3,6] If conservative treatment fails patients present with a recurrence of high risk bladder cancer with or without progression, the most common therapy is radical cystectomy. The exact timing of this cystectomy is still unclear and subject of many studies. Despite the presence of guidelines towards management of bladder cancer of the American and European Urological Associations, the actual management shows quite large variation. A great majority of surveyed urologists in the USA in 2003 were still reluctant to perform a cystectomy in patients with a high grade tumor who failed intravesical immunotherapy although this was described in the guidelines and a cystectomy in this group of patients gives a tumor-specific survival of 80 – 90 %.[7]

In the Netherlands a national guideline for diagnosis and treatment of bladder cancer is available since 2009. Until that moment regional consensus based guidelines are available within the regional comprehensive cancer centers. The current clinical practice roughly matches the European Association of Urology guidelines.[8,9]

Pattern of care studies are used to identify disparities in patient treatment. These studies can also evaluate which tumor related, patient related or other factors determine the treatment decisions and how this could influence the course and development of the treatment outcome.[7,10,11]
The aim of this retrospective study was 1. To evaluate the actual pattern of care in patients with newly diagnosed high risk NMIBC in the CCCN and 2. To assess factors associated with the choice of treatment, 5 year recurrence and progression free survival rates.

Material and methods

Selection

From the cancer registry of the CCCN a total of 535 patients identified with a first manifestation of NMIBC in the period 1997-2002. We selected all cases with a non muscle invasive urothelial cell carcinoma stage Ta/1 G3 with/without CIS or isolated CIS of the bladder. Patients with metastatic disease (n=5) and TxG3 (n=8) were excluded. From 110 patients the medical records were not available for data collection on follow up and recurrence. The final analytic cohort included 412 patients with high risk NMIBC of the bladder.

Data collection by the cancer registries

Data were collected by the regional cancer registry of the CCCN. Within the CCCN a total of 15 hospitals participated including one University Medical Center and 3 major teaching hospitals. The nationwide Dutch network and registry of histo- and cytopathology regularly submits reports of all diagnosed malignancies to the cancer registries. Trained registry personnel collect data on demography, diagnosis, staging, comorbidity, treatment and follow up from the medical records, including pathology and surgery reports. Treatment was coded in sequence of administration to a maximum of four treatment modalities. Vital status was established either directly from the patient's medical record or through linkage of cancer registry data with the municipal population registries. Stage was based on pathological information of primary tumor or first recurrence. CIS is only registered as CIS in case of isolated CIS; concomitant CIS is included in the group Ta/ T1G3 tumor. BCG-failure was defined as recurrent disease in patients who were treated with a first course of 6 instillations of BCG. Teaching hospitals were defined as hospitals which provide training for residents to become urologist. We analyzed the retrospective data anonymously and therefore no formal ethical committee approval was needed. The local oncology committees have granted permission to examine the medical files of the included patients for additional data which were collected.

Statistics

To assess the factors associated with choice of treatment we used a logistic regression analysis. Time to local recurrence is defined as the time from diagnosis to the registered histological proven recurrence in the bladder after prior treatment. Progression time is defined as time from diagnosis to any registered recurrent tumor with progression in T-stage, arising concomitant CIS or progression to lymph node or distant metastases. Differences in 5 year Recurrence Free Survival (RFS) and Progression Free Survival (PFS) were assessed using the log-rank test. The effect of several factors on 5 year RFS and PFS were studied using a multivariable Cox regression analysis. As cause of death was unknown in 19.8% of the patients we choose to use relative survival. The relative survival has been shown to be a good estimator of the disease specific survival in absence of information on the cause of death or in case information on the cause of death is inaccurate.[12] The relative survival estimates the net bladder cancer survival, survival in the hypothetical situation that bladder cancer is the only possible cause of death. Survival time was calculated from the date of diagnosis and ended at the date of death, or the date of last contact, or the date of most recent linkage with the municipal population registries and/or national death registry, whichever came first. Maximum follow-up was curtailed at to 8 years. Relative excess risks of death (RER) were estimated using a multivariate generalized linear model with a Poisson error structure, based on collapsed relative survival data, using exact survival times.[13]

Results

Treatment

Overall, 18% of the 412 patients with a high risk NMIBC underwent a TUR as single treatment (Table 1). Seventy-seven percent of the patients received adjuvant treatment with a single immediate Mitomycine C (MMC)-instillation, MMC-instillations or BCG-instillations with or without a prior single MMC-instillation (3.3 %, 39 % and 34 %, respectively).
For the assessment of associating factors in the choice for TUR with adjuvant therapy 20 patients were excluded because of any other treatment.
As shown in Table 2, younger patients more often received adjuvant therapy (p=0.001); patients younger than 60 years received adjuvant therapy in 92.2% of the cases and only 71.4% of the elderly patients (≥75 years) did

Patient Charateristics		Number	Percentage
Sex	Male	354	85.9
	Female	58	14.1
Age category	< 60 years	68	16.5
	61 - 74 years	198	48.1
	> 75 years	146	35.4
Period	1997-1999	197	47.8
	200-2002	215	52.2
Comorbidity	None	115	27.9
	One	159	38.6
	Two or more	138	33.5
Treatment	TUR	76	18.4
	TUR with single instilation	14	3.4
	TUR+ chemotherapy	160	38.8
	TUR+BCG	142	34.5
	Cystectomy	16	3.9
	Radiotherapy	4	1.0
Hospital	Non-teaching	220	53.4
	Teaching	192	46.6
Stage	TaG3	125	30.3
	T1G3/4	258	62.6
	CIS	29	7.1

Table 1 Characteristics

Variable		Number	TUR+adj	analysis		Multivariate analysis	
				p-value	OR	95%CI	p-value
Sex	Male	339	80.2				
	Female	53	83.0	0.634			
Age	< 60	64	92.2		ref		
	61-74	188	83.5		0.40	0.15 -1.11	
	> 75	140	71.4	0.001	0.22	0.08 -0.59	0.004
Comorbidity	None	108	81.5				
	One	152	80.9				
	Two or more	132	79.6	0.924			
Hospital	Non-teaching	209	71.8				
	Teaching	183	90.7	< 0.001			
Stage	TaG3	122	82.8				
	T1G3/4	241	78.4				
	CIS	29	89.7	0.269			
	1997-1999	186	78.0				
Year	2000-2002	171	83.0	0.206			

Table 2 Factors associated with the choice for TUR+adjuvant therapy

receive adjuvant therapy. Besides, in teaching hospitals 90.7% of the patients received adjuvant treatment after the TUR compared to 71.8 % in patients treated in non-teaching hospitals (p<0.001). In multivariate analysis, older age (61-74 years OR 0.40 (0.15-1.11) and 75 and older OR 0.22 (0.08-0.59); p=0.004) and treatment in non-teaching hospitals (OR 3.61; p<0.001) were associated with less adjuvant treatment after TUR.

Progression-Free Survival

Local recurrence was observed in 191 of the 392 patients (48.2%) with their bladder in situ during a mean follow up of 2,7 years (range 0,1 – 9,2). Of the 76 patients treated with TUR alone 44 (58%) showed recurrent disease versus 147 (49%) of the 316 patients treated with adjuvant chemo or BCG therapy showed recurrent disease (HR 0.66; p=0.02). Median time to local recurrence was 2.6 years (range 0.10-9.20). None of the other variables sex, age, comorbidity, teaching/non-teaching hospitals, stage, year or treatment was associated with local recurrence (data not shown).

Tumor progression occurred in 84 of the 392 patients (21.4%). The mean 5-years progression free survival was 71.6% (95% CI 65.5-76.8).

In multivariable analysis disease progression showed a trend towards significance with stage (adjusted for age and type of growth) with an HR of 0.97(95% CI 0.60-1.56) for T1G3/4 (as opposed to TaG3) and a HR of 0.13 (95% CI 0.02-0.97) for CIS with a p-value of 0.1. None of the other registered factors was statistically significant associated with progression-free survival.

Relative survival

During a median follow up period of 4,5 years (range 0,1 – 8,0), 164 of the 412 patients (39.8%) died. The 5-years relative survival was 81.9% (95% CI 75.2-88.0). Patients with one or more comorbidities appeared to have a lower survival (5-years relative survival 70.8%) than patients with no comorbidity (95.2%; p=0.084). None of the other registered factors was significantly associated with relative survival in either univariate or multivariate analysis.

BCG-failure

Of the 142 patients initially treated with BCG 76 patients (54%) failed after first course of BCG. Patients with CIS alone (42.9%) treated with BCG failed somewhat less often than patients with TaG3 (52.9%) or T1G3 (55.8%) with or without CIS (p=0.4). BCG failure appeared to occur more often in patients with two or more comorbidities (HR 1,38 p=0.2). Histology was not associated with BCG failure. Two third of the failures were still non muscle invasive tumors (53/76). Nine of the patients were treated with a cystectomy (17%), while 26 were treated with a second course of BCG (34%).

Discussion

In this pattern of care study for high risk NMIBC we found hospital type and age to be associated with the choice for adjuvant treatment. Both age and comorbidity appeared to influence progression-free and relative survival, but no other clinical factors were associated with progression, survival or BCG failure. The treatment of patients with high risk NMIBC in the Northern Netherlands in 1997 – 2002 does not differ much of the daily urologic practice in Europe or US.

In 1999 the AUA (American Urological Association) Bladder Cancer Guidelines Panel recommended intravesical chemotherapy as a treatment option after endoscopic removal of low-grade Ta bladder cancer and intravesical BCG or MMC for CIS and after endoscopic removal of T1 and high grade Ta tumors.[14] Later in 2004 Sylvester showed a lower rate of recurrence in patients who received intravesical therapy within 24 hours postoperatively.

Worldwide the preference for TUR as single treatment for high risk NMIBC decreased throughout the last decade. In a pattern of care study by Snyder et al, 40% of the patients who were diagnosed in 1995 with a high risk bladder tumor underwent resection only.[11] In our cohort, few years later, 18 % did not receive adjuvant therapy.

Remarkably in a pattern of care project of the SEER program of 2003, data suggest still an underuse of intravesical therapy in patients with high risk NMIBC. Only 42 % of the high risk patients received intravesical therapy. Apparently barriers to the application of this therapy are not clear yet.[10]

The proportion of patients not receiving adjuvant therapy is very high compared to opinions expressed by urologists in recent survey studies. Witjes (2005) noticed that 94,6 % of the Flandran and Dutch urologists would offer high risk patients at least an instillation course, predominantly BCG.[15] This difference could also express any changes in clinical practice in our region since 2002. And also in the US in a survey in 2003 18 % of the urologists state to prefer TUR only for Ta-T1 high grade tumors and 8 % and 1 % for concurrent CIS and CIS only respectively.7 This difference in results between a survey study and a pattern of care study might be explained by self-selection of urologists that respond to questionnaires while the actual practice of all urologists is evaluated in a pattern of care study. Adjuvant treatment after TUR was performed significantly more common in teaching

hospitals (59/220= 26.8%) than in non-teaching hospitals (17/192=8.8%). In the middle of the nineties several randomized clinical trials were published which showed a significant effect of adjuvant treatment with respect to at least the time to recurrence.[16,17] Apparently it takes some time to implement these findings as changes into treatment protocols.

We found 49 % (191/392) recurrences in the patients treated with adjuvant treatment after TUR. The percentage of progression found in this high risk group roughly matches the figures presented in literature.[1,3,6,18–22] Differences in the kind of adjuvant treatment did not appear to affect the progression rate. However, in our study it is not clear what percentage of patients treated with BCG really received long term maintenance therapy. Böhle et al. demonstrated in a meta-analysis of comparative studies for BCG versus MMC a significant superiority for BCG for the prevention of tumor progression only if BCG maintenance therapy was provided.[1] In a sub-analysis Sylvester also showed superiority of BCG maintenance to MMC for patients with Tis.[3] In the phase 3 study 30911 of the EORTC intravesical BCG with or without INH showed to be superior to intravesical epirubicin not only for time to first recurrence but also for time to distant metastases, overall survival, and disease-specific survival. A clear overview of meta-analyses of studies comparing intravesical therapies and differences was published by Hall et al in 2007 in an update of the guideline for the management of NMIBC (Stages Ta, T1 and Tis).[14] The individual patient data meta-analysis by Malström in 2009 showed again the superiority of BCG in the prevention of recurrences. Prior intravesical chemotherapy was not a confounder.[23] Differences in outcome may be explained by heterogeneity of included patients, different chemotherapeutical agents which are used and different durations of therapy.

Because of concurrent CIS in the papillary tumor groups it is very difficult to draw any conclusion about the separate effect of stage. Also there is limited inter- and intra-observer agreement in histological examination which affects the appropriateness of the staging. In a review pathology study the overall conformity in stage was only 50-60 %, largely due to non-agreement for the low-stage tumors. Stage T1 and CIS appear to be the most difficult entities to determine while the differentiation of these tumors is important in the decision regarding conservative or more aggressive therapy.[24]

The 5-year relative survival is 81% whereas almost 40% of the patients died during follow up. Many patients probably died of other causes than their disease. It is obvious that multiple co morbidities are associated with a worse relative survival. A retrospective study in 2002 on T1G3 tumor patients also did not find significant differences in survival between patients treated with BCG and transurethral resection alone.[25]

Many recent studies on T1G3 bladder tumor treated with BCG showed recurrences of 23 to 52 %.[1,6,18,19,21,22] The number of patients treated in those studies did not exceed 81, but the median follow up was longer than in our retrospective study. No difference was observed between groups of patients treated with or without the maintenance protocol after the induction therapy with BCG. Our study showed similar results with a recurrence rate of 54 % and a progression rate of 16 % in 142 patients who were treated with BCG. Though we will stress that there will be confounding by indication bias as it is a retrospective study.

Nowadays there is a tendency towards early cystectomy for recurrent T1 disease during or following intravesical BCG therapy. This may be associated with better disease specific survival. Some investigators promote immediate cystectomy for T1G3 tumors.[26] In our series 5,0 % of the T1G3 tumors were treated with radical cystectomy after the diagnostic TUR. This is conform to the results of Joudi et al. were 7 % high risk patient underwent radical cystectomy.

Besides promising salvage therapies for patients unsuitable for radical cystectomy are awaited in the near future. As Yates et al. published very recently an update of the application of thermochemotherapy, intravesical interferon-alfa and electromotive drug administration.[27]

This pattern of care study accurately reflects the former daily practice in this CCCN region and the consequences for recurrence and progression free survival. One of the limitations is that it is not possible to assess specific determining factors in individual patients or in individual hospitals. Therefore prospective research should not focus on these particular factors but more on the background of the choice between different therapies.

Conclusion

In this pattern of care study in high risk NMIBC, older age and treatment in non-teaching hospitals were associated with less adjuvant treatment after TUR. Differences in treatment did not significantly affect 5 year recurrence free and progression free survival rates.

None of the variables sex, age, comorbidity, teaching/non-teaching hospitals, stage and year or treatment was associated with 5 year local recurrence or with progression rates. Comorbidity was associated with a lower relative survival.

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EDITORIAL COMMENT

The authors examined 412 patients (diagnosed between 1997-2002) within the North-Netherlands Cancer Registry for variation in the use of adjuvant therapy in patients with high risk superficial bladder cancer (defined as high grade Ta/T1 or CIS). 82% of patients received some form of adjuvant ravesical therapy. Of patients receiving adjuvant therapy, 4% received only a single peri-operative installation, while induction BCG or chemotherapy was given in 45% and 51% of patients, respectively. It is unclear from the presented data what proportion of patients receiving induction therapy also received a peri-operative dose. Overall, these results suggest a much higher rate of compliance with published treatment guidelines than that found in similar studies in the Unites States (ref. 10 and 11 in article). Surprisingly, increasing age, but not co-morbidity, was significantly associated with lower odds of intravesical therapy use. Contrary to the findings of Huang et al. (ref. 10), the use of adjuvant intravesical therapy was greater in teaching versus non-teaching hospitals in the Netherlands.
Because the first AUA guidelines were published in 1999 [1], and the first EAU guidelines in 2002 (ref. 8), it will be interesting going forward to re-examine these findings as further dissemination has hopefully occurred. In addition, newer guidelines by the AUA (ref. 14) and EAU[2] emphasize re-resection of high grade T1 lesions (even with muscle in the initial specimen) as well as the use of maintenance therapy. It will also be important to examine compliance with these newer guidelines. Finally, while the identification of factors associated with decreased intravesical therapy use age, ethnicity, or type of practice gives clues as to the barriers preventing implementation, the main underlying issues may be failure to disseminate existing literature, patient burden (perceived or real), and logistical issues which affect provider work-flow.

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EDITORIAL COMMENT

From a distance, it may look as if there is nothing new under the sun regarding management of non-muscle invasive transitional cell bladder cancer. We use urine cytology, transurethral resection, intravesical doxorubicin or mitomycin and BCG for more than 35 years and they remain our main weapons for fighting not only costly (due to innumerous recurrences), but unpredictive and if progressive often fatal disease.
At a closer look, the field of this disease has changed quite significantly in recent years. Without considering new markers, drugs and techniques which are already available it may look promising in the future (studies evaluating screening with combinations of new markers like FISH analysis of exfoliated cells in urine, proteomics, fluorescence blue light cystoscopy and resection, gentamycin, microwave heated or electromotive intravesical drug application). Main change has been in standardization and systematization of our approach to patients with this disease. Those changes took place in recent years and guidelines (AUA, NCCN and EAU) are all freely available from their respective websites. AUA guidelines are quite narrative and give reasoning behind suggestions, NCCN produces and every few months updates short and up to a point graphic algorithms decision trees and EAU may has produced (in their last, 2009 update) most precise and straightforward set of rules for dealing with non-muscle invasive bladder cancer.
EAU rules seem to have almost taken "art" out of medicine in this area and "science" has almost completely taken over. Is this good? The present article by Leliveld and coworkers shows us the importance of this aspect. Although titled "High risk bladder cancer: current management and survival", they report only 35% of patients who were only treated some 8 years ago (in 2002), in a western European country, according to present regional (EAU) guidelines. This means 65% of high risk superficial bladder cancers have not received immunotherapy (BCG), which they, according to present guidelines, should have received. Although the authors in discussion address this issue and cite one, 8 year old study, which claims no survival advantage for immunotherapy group and this may be debatable, the fact still remains solid: majority of patients were at the time of study not treated according to present guidelines. Some patients may be unsuitable (too old etc.) for treatment according to guidelines and guidelines have room for improvement with specifically addressing those marginal groups. Perhaps some patients may be in a registered clinical trial (this is not reported). But otherwise current management of high risk bladder cancer should not be

as was mentioned in this study. If not for other reasons, guidelines take a lot of hesitation out of our mind and help us a lot in ultimate question with high risk patients i.e. to proceed with cystectomy or continue conservative treatment? Decision for cystectomy is a difficult one and it is universally accepted it is often made too late.[1] Relatively rigid guidelines offer a highway towards this decision, if and when needed. Although guidelines can and will change with time, obeying them is a first step towards improving outcomes, which for bladder cancer seem to remain the same for decades with no improvement. Only years after we have standardized our approach and try to follow guidelines with each individual patient, SEER and other cancer statistics may and will reflect improvements.

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Chapter 2