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Relevance of Repeat Transurethral Resection of the Bladder for High Grade pTa Bladder Cancer: A Review

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Abstract

Repeat transurethral resection of the bladder (reTUR) is highly recommended for high risk non muscle invasive bladder cancer. The evidence are strong for high grade pT1 tumors, but scarce for high grade pTa. In this systematic pubmed review, we analyzed the performance of reTUR for high grade pTa bladder cancer in terms of rate and characteristics of residual tumors. Data on survival was also retrieved and we provided meta-analysis figures on what to expect with such approach.

ReTUR retrieved residual tumors in about half of the cases with upstaging to muscle invasive disease in almost 2%. Data were nonetheless insufficient to state on the relevance of reTUR high grade pTa. Based on analyzed data, we suggest to offer systematic reTUR for incomplete or muscle lacking initial TUR. For other high grade pTa tumors, a second look TUR shall be an option to be discussed at MDT meeting, based on the use of HAL or NBI at first TUR, the experience of the surgeon, and whether the patient would be fit for a close surveillance or additional treatments.

Keywords: Urinary bladder neoplasms; Second-look surgery; Neoplasm; Residual; Repeat resection; Transurethral resection of the bladder

Introduction

Non Muscle Invasive Bladder Cancer (NMIBC) are initially best managed using transurethral resection of the bladder (TUR) aiming to provide adequate staging and tumor removal [1]. Although TUR is widely used among urologists its efficacy is limited. Disease persistence or understating of High Grade (HG) pT1 tumors has been reported as high as 72% and 29% respectively [2]. TUR should therefore be seen as an incomplete procedure in most cases that requires additional measures to improve the chance of cure.

Repeat transurethral resection of the bladder (reTUR) performed a few weeks after the initial TUR has clearly proven to reduce the risk of recurrence for pT1 high risk NMIBC [3]. It improves local control and response to BCG [4] and identifies a significant number of patient with muscle invasive bladder cancer for which more invasive treatments are required. As a result, reTUR has become the cornerstone of high risk NMIBC management and is strongly recommended by urology guidelines [1,5].

The NMIBC high risk group also includes high grade pTa, and reTUR is recommended all the same for this group although literature evidence is scarce to validate such approach. There is even some controversy on whether reTUR should be offered for HG pTa cancer since the risk of progression in this subgroup is much lower than for the pT1 group [6]. It is also unknown whether early reTUR improves survival or quality of life compared to delayed TUR at the time of a recurrence that would be spotted during surveillance.

We therefore aimed to review published literature to analyze the impact of reTUR for HG pTa bladder cancer in terms of residual tumor yields, stages, morbidity, cost and survival and provide overall meta-analysis figures on what to expect with such approach.

Methods

A Prisma systematic review of the literature was performed in august 2016 using Pubmed with the following criteria:*("Urinary Bladder Neoplasms"[Mesh] OR "bladder cancer") AND ("re-resection" OR "second look" OR "second TURB" OR "second resection" OR "persistent disease"*

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Table 1: Summary of all studies reporting reTUR results for high grade or mixed grades pTa bladder cancers.
Single figures represent the number of patients. Figures in bold relates to the pTa category analyzed.
N/A: Not Analyzable; HG: High Grade Tumors or G2G3 tumors
*the first percentage relates to residual tumors only and the second to the total of patient who had reTUR.a

Studies	NMIBCa	pTa	HG pTa	Re-TUR (%)	Residual Tumor (%)	pTa/Tis (%)	pT1 (%)	pT2 (%)	Overall upstaging (%)	Recurrence
Studies with HG pTa data analysed										
Gendy et al. 2015 [8]	1209	631	218	37 (17%)	26 (70%)	24 (92%)	1 (4%)	1 (4%)	2 (8%)	57% ReTUR 83% no ReTUR
Herr & Donat 2006 [9]	710	463	327	327 (100%)	218 (67%)	190 (87%)	28 (13%)	N/A	28 (13%)	N/A
Lazica et al. 2013 [13]	912	616	142	87 (61%)	36 (41%)	31 (86%)	5 (14%)	0 (0%)	5 (14%)	N/A
Vasdev et al. 2011 [7]	64	64	64	49 (77%)	24 (49%)	17 (71%)	5 (21%)	2 (8%)	7 (29%)	13% ReTUR 53% no ReTUR
Cao et al. 2015 [10]	134	75	35	35 (100%)	15 (43%)	N/A	N/A	N/A	N/A	N/A
Han et al. 2008 [12]	56	25	22	22 (100%)	15 (68%)	13 (87%)	1 (7%)	1 (7%)	2 (13%)	N/A
Guevara et al. 2010 [11]	117	18	18	18 (100%)	5 (28%)	N/A	N/A	N/A	N/A	N/A
Liu et al. 2015 [14]	72	17	17	17 (100%)	7 (41%)	N/A	N/A	N/A	N/A	N/A
Fujikawa et al. 2012 [15]	111	58	9	9 (100%)	6 (67%)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	N/A
Holmang et al. 2013 [27]	164	66	66	10 (15%)	N/A	N/A	N/A	N/A	N/A	2/10 (20%) ReTUR + BCG 6/56 (10%) no ReTUR + BCG
Total pure HG pTa	3549	2033	918	611 (67%)	352 (58%)	275 (85%-51%*)	40 (12%-7%*)	4 (3,7%-2%*)	44 (14%-8%*)	
Studies with mixted pTa analysed										
Zurkirchen et al. 2004 [21]	214	99	N/A	99 (100%)	27 (27%)	22 (81%)	5 (19%)	0 (0%)	5 (19%)	N/A
Grimm et al. 2003 [19]	194	90	N/A	61 (68%)	17 (28%)	N/A	N/A	N/A	N/A	N/A
Schips et al. 2002 [20]	110	31	N/A	31 (100%)	12 (39%)	10 (83%)	2 (17%)	0 (0%)	2 (17%)	N/A
Ali et al. 2010 [16]	91	30	N/A	30 (100%)	12 (40%)	6 (50%)	6 (50%)	0 (0%)	6 (50%)	N/A
Bishr et al. 2014 [17]	94	29	21	29 (100%)	15 (52%)	N/A	N/A	2 (13%)	2 (13%)	56%
Gill et al. 2014 [18]	52	27	N/A	27 (100%)	12 (44%)	8 (67%)	3 (25%)	1 (8%)	4 (33%)	N/A
Total Mixed pTa	755	306		277 (91%)	95 (34%)	46 (73%-25%*)	16 (25%-9%*)	3 (3,8%-1,4%*)	19 (24%-9%*)	
Total All Studies	**4304**	**1224**		**888 (73%)**	**447 (50%)**	**321 (83%-45%*)**	**56 (14%-8%*)**	**7 (3,8%-1,7%*)**	**63 (14%-7%*)**	

OR "Neoplasm, Residual"[Mesh] OR "re-staging" OR "restaging" OR "repeat transurethral resection" OR "repeated transurethral resection" OR "relook" OR "second-look surgery"[MeSH Terms]) AND English[lang] NOT (Editorial[ptyp] OR Review[ptyp] OR Letter[ptyp] OR Comment[sb] OR News[ptyp]).

We retrieved 257 articles in July 2016. Further selection of relevant articles was based on title, abstract and finally full paper content analysis. Studies not including HG pTa tumors or studies providing results mixing pTa and pT1 tumor results were discarded. Any study providing either the rate of residual tumor or recurrence rates for HG pTa were included. Studies in which HG and LG pTa reTUR results were provided but mixed together were also selected but analyzed separately. Further analysis of AUA, NICE and EAU guidelines references and a similar criteria search focusing on reviews only (n=63) was performed and retrieved one more article [7]. We finally identified 16 articles among which 10 had detailed results for HG pTa [7-15] and 6 with detailed results on a mixed group of low and high grade pTa [16-21].

The stage of residual tumors was reported as a percentage of all patients who had residual tumor on reTUR and for which the stage at reTUR were reported. This explains why the sum of percentage in the summaries is not 100%. Data on pT is on reTUR were merged with pTa tumors in most of the publications and provided in the same way for this review.

Results

Risk of residual disease on reTUR for HGpTa

Results are summarized in Table 1. Series including detailed data for HG pTa reported the presence of residual disease on reTUR for 58% of the cases, ranging from 28% to 68%. In series for which LG and HG pTa were analyzed together, the residual tumor rate was lower (34% [27-52%]). This could possibly reflect the poor relevance of reTUR for Low Grade (LG) pTa although the rate of HG pTa for each series was unknown except for one [17]. In this study, authors reported 82% of HG pTa and a residual tumor rate of 52% for all pTa mixed together. As a matter of comparison, residual tumor rate on reTUR for LG pTa was also provided in two studies of the review [10,15] showing that among 49 and 40 LG pTa who had reTUR, 17 (35%) and 7 (18%) had residual tumors.

Many factors can influence residual tumor rates at reTUR [22],

especially the quality of the surgical technique used to perform the initial TUR and its extension and depth. Surgeon's technique and experience is of importance since less recurrences were observed for patients operated by senior urologist compared to residents (Jancke, Rosell et al. 2014). Another related key factor is the presence of detrusor on pathological reports confirming the initial TUR was deep enough. This was not reported for pTa in most of the studies included in this review [7,9,13,16-18,20,21,23]. Moreover, many did not report whether all the patient included had a complete initial TUR [7,9,12,13,17,21], and one series reported having included 12% of incomplete initial TUR [16].

No studies reported on the performance of reTUR if the initial TUR was followed by a single post-operative instillation of mitomycin or performed using Narrow Band Imaging (NBI) or hexylaminolevulinate acid (HAL). Although mitomycin in the context of HG tumor is considered inapropriate, both NBI and HAL have shown to reduce the risk of recurrence [1]. One randomized study including HG pTa and pT1 compared white light reTUR to NBI reTUR. All patients had white light TUR for the primary tumor. Patients in the NBI reTUR had less recurrence at 2 years compared to white light reTUR (22% *vs.* 33%), but the study was underpowered and no data was available for HG pTa only. Similarly, another randomized study compared HAL TUR to white light TUR followed for both arms by white light cystoscopy [24]. HAL arm had less recurrence and progression but no data could be extracted regarding HG pTa.

Other factors may also influence residual tumor rates such as the number of tumors resected and their size. These were poorly reported for the pTa sub group. The tumor size was never reported and the multifocality was only reported in two studies (14% [20] and 24% [19]). Nonetheless, one study including only large (>3cm) or multiple NMIBCa, reported the presence of residual macroscopic tumors at 3 months cystoscopy in 43.7% in a population of various grades pTa that did not have reTUR [25]. This rate is comparable to the 51% found for the mixed pTa population (Table 1).

Molecular factors may also influence the likelihood of residual tumor on reTUR. Liu et al. [14], showed that tumor size, multifocality but also p53 and E-cadherin expression are risk factors of residual tumor at reTUR in a NMIBCa population. Such a marker panel may help to identify patients with non-muscle-invasive bladder cancer who are likely to have residual tumor after the first TUR and therefore benefit from reTUR.

Finally, all series were retrospective and did not report clearly on criteria triggering a reTUR nor did compare with pTa patients that did not have a reTUR except two [7,8]. These limits have to be taken into consideration and may result in significant differences in reTUR tumor rates within centers and these results may not apply to a population including all HG pTa.

Risk of upstaging on reTUR for HG pTa bladder cancer

ReTUR mainly serves one overarching purpose: to identify patients with MIBCa who have been under staged by an inadequate first TUR and would be inadequately treated without a reTUR.

When residual tumors were found on reTUR for HG pTa, a similar stage was the most common occurrence. In the HG pTa series, pTa stage represented 85% (71%-100%) of the residual tumors, and 73% (50%-83%) for mixed pTa series.

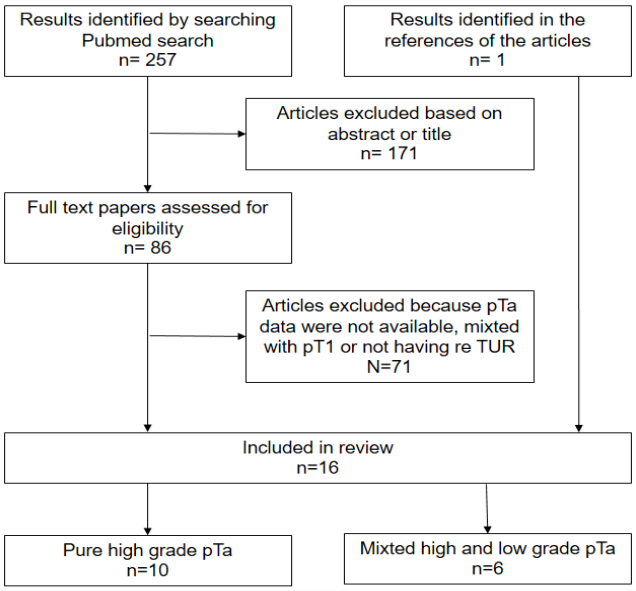

Figure 1: Chart flow summarizing literature search strategy and results.

Regarding upstaging, although pT1 on reTUR was common and occurred in 12% (0%-14%) for HGpTa and 25% (17%-50%) for mixed pTa, upstaging to pT2 on reTUR was rare, occurring in 4% (0%-13%) for both series.

It is remarkable that mixed series had a higher rate of upstaged tumors than pure HG pTa series although they included some LG pTa. As mentioned above, the presence of muscularis propria in the sample was poorly reported by the authors although this is of paramount importance to assess the technical quality of the TUR. This may have had a role in the difference observed possibly explained by more superficial TUR in the mixed pTa series. Nonetheless, it was not possible to clarify this hypothesis in the studies.

The stages provided in these studies were also not reviewed by multiple uro-pathologists. In a pathological review of samples collected in 5 EORTC trials, agreement among pathologists was low, reported to be only 57% for G1 pTa and even lower (50%) for G3 pT1, [26]. The pathology review down staged 53% of the tumors originally classified as pT1 to pTa. Such variations in the assessment of the pathological stage may support the hypothesis that a significant proportion of pTa that were upstages following reTUR may actually be the result of initial TUR that were not deep enough or pT1 tumors reported as pTa.

Nonetheless, upstaging to pT1 is unlikely to be a major issue since management of HG pTa and pT1 bladder cancer follow similar principles [1,5].

More of a concern is pT2 upstaging on reTUR. The risk of pT2 upstaging represented 4% of the residual tumors, but this was only 1.7 % of the 420 patients who had a reTUR (whatever the result) and for which the data about pT2 upstaging was available. These results are consistent with the recent EORTC nomogram for NMIBCa treated with BCG and maintenance. None of the patient had reTUR in the EORTC studies included. It showed that the 1 year progression rate for HGpTa was 1.8% [6]. Since BCG is poorly effective when residual tumor is left in place (especially for pT2 tumors), it can be hypothesize that this early progression rate is the result of under diagnosed pT2 tumors. Of interest is also the progression rate for LG pTa in this

study which was very similar (1.9% and 1.6 % for G1 pTa and G2 pTa/G1 pT1 respectively). This suggest that the pT2 upstaging risk is almost the same for HG pTa than LGpTa. Although pT2 upstaging is of paramount importance since the management of muscle invasive disease requires a much more invasive approach, it is questionable to perform a systematic reTUR for all HG pTa (as suggested by guidelines) since the pT2 upstaging risk may to be quite similar for the whole pTa group.

What is the risk of recurrence and progression with or without reTUR for HG pTa bladder cancer

Outcomes following reTUR were available in three studies that compared reTUR and no reTUR arms for HGpTa tumors. Gendy et al. [8] had a recurrence rate of 57% with reTUR compared to 83% without, after a short follow-up of 3 to 6 months[13]. Although it appears to be a strong difference between arms, the depth and quality of the TUR were probably not optimal since only 36% of the specimen had muscularis propria on pathological reports at initial TUR. This would also explain that even in the reTUR arm, recurrence rates were much higher than in another study from Vasdev et al. [7] who reported recurrence rates of 13% with reTUR and 53% without after 49 months. Differences in term of recurrence rate within studies may have been explained by the quality of the initial TUR and the administration of BCG, both in favor of the second study. In a third study, authors reported less recurrences for patients not having had reTUR (20% and 10% with and without reTUR) and both arms received BCG [27]. Unfortunately no data were available regarding residual tumor rates and stages in the reTUR arm.

All studies were retrospective, limited in size, without strict criteria triggering the reTUR. The evidence are therefore insufficient to draw any conclusion. Nonetheless, it is noteworthy that in these studies, residual tumor rates were very close to recurrence rates in the no reTUR arms(70% *vs.* 83% and 49% *vs.* 53% respectively), suggesting that most of early recurrences are related to the presence of residual tumor following the initial TUR.

Performing a reTUR in the pTa group is likely to reduce further recurrence, but areTUR would be relevant only if it reduces the risk of progression to muscle invasive disease or improves cancer specific survival. None of the study reported on muscle invasive progression during surveillance, but follow up was very limited for the first study and concerned only 46 patients for the second. In this later, no cancer specific deaths were recorded after 49 months.

Sfakianos et al. [28] reported updated survival outcome results of a large series of 1021 high risk NMIBCa [28] including some selected for this review published earlier [9]. Unfortunately, specific results for the HGpTa that represented 60% of the cohort were not available. Authors found that reTUR for high risk NMIBCa did not reduce the risk of recurrence at 5 years when early recurrences were excluded (within 3 months) compared to patients who did not have reTUR (57.5% *vs.* 58.3% respectively).This study confirmed that there was a reduction of the risk of progression for the entire cohort, but no results were available for pTa tumors. This is likely to be biased by the impact of reTUR on HGpT1 [3] and a potential benefit of reTUR on HG pTa remains to be clarified.

Intravesical therapy is most effective when used against minimal residual disease and is unlikely to eradicate macroscopic residual tumors. Nonetheless, in a retrospective study including 56 newly diagnosed G3pTa treated with BCG, post BCG recurrence occurred for 2 out of in 10 patients who had reTUR (20%) compared to 10% for those 56 patients who did not have reTUR [27]. None had progression. Authors concluded that a routine re-resection may be unnecessary. Other authors have suggested that reTUR could improve BCG response with the occurrence of lower grade tumors at recurrence if reTUR did not harvest any tumor [11,14]. In this case, reTUR would only be useful as a prognostic factor.

Overall, studies rarely analyze separately early and late recurrence regarding the role of reTUR and its potential impact on intra-vesicle therapies, and no conclusion could be drawn on the benefits of reTUR on BCG response or progression for the HG pTa group.

Cost, morbidity and relevance of a reTUR

In terms of complications related to reTUR for HG pTa, no data were available. In a study, only one out of 254 patients was returned to the operating room for post-operative bleeding following reTUR for high risk NMIBCa including 63% of HG pTa [29]. Another large series reported that 2.8% of the patients will have bleeding complications and 1.3% bladder perforation [30]. It is nonetheless likely that reTUR may lead to less bleeding complications, since these are related to the size and the number of tumors resected [30]. On the contrary, one could suspect that reTUR may not lead to a lower rate of bladder perforations. Less severe bladder injuries (0.3% *vs.* 0.6%) were reported with the use of bipolar instead of monopolar TUR [31] and may be used for patient undergoing reTUR.

No data were available regarding the cost of reTUR and we found no medico economic studies on reTUR for HG pTa only. One randomized study assessed HAL TUR for NMIBCa including 78% of mixed grade pTa tumors in which all patients had reTUR [24]. Cost analysis was in favor of performing HAL TUR followed by reTUR, but no conclusion could be drawn for HG pTa.

Since the risk of misdiagnosing a muscle invasive tumor for HG pTa is rare following the first TUR, it is questionable whether a reTUR for all patients is relevant compared to performing a TUR when a recurrence is observed following surveillance. Performing a reTUR for all patients could be seen as an overtreatment since only half of the tumors have residual tumors on reTUR, resulting in an increased cost and increased risk of complications. It is also unknown whether the almost 2% of patients found with muscle invasive disease at reTUR would have been missed if reTUR would have been performed only for incomplete initial TUR or for those lacking muscularis propria. Moreover, HAL or NBI initial TUR although not available in all centers is recommended and likely to minimize the relevance of performing a systematic reTUR.

ReTUR is a generic procedure that encompass various situations that should be define more precisely. New TUR performed because the initial one was incomplete or lacking muscularis mucosae we suggest it should be described as “complementary resection” or “restaging resection” respectively. Excluding these two situations, when the TUR is repeated because of the high risk of residual disease or under staging based on stage or grade, we suggest it should be described as “second-look resection” to remain in line with the MeSH term “second-look surgery”. In this review it was not possible to differentiate the type of reTUR. Future studies on reTUR should differentiate thesevarious situations. Moreover, this review highlighted the importance of early versus late recurrence/progression and here again further studies may benefit from analyzing this data separately.

Conclusion

ReTUR retrieved residual tumors in about half of the cases with upstaging to muscle invasive disease in almost 2%. Data were nonetheless insufficient to state on the relevance of reTUR for all HG pTa. Based on analyzed data, we suggest to offer systematic reTUR for incomplete or muscle lacking initial TUR. For other HG pTa tumors, a second look TUR shall be an option to be discussed at MDT meeting, based on the use of HAL or NBI at first TUR, the experience of the surgeon and whether the patient would be fit for a close surveillance or additional treatments. Further studies including all these aspects are required to clarify whether reTUR shall be offered routinely for all HG pTa.

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