OPTIMAL PATHOLOGIC RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER: RESULTS FROM A GLOBAL, MULTI-CENTER COLLABORATION

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ABSTRACT

Objectives*:* To evaluate outcomes of patients achieving <ypT2N0 disease at radical cystectomy (RC) following neoadjuvant chemotherapy (NAC) for muscle-invasive bladder cancer (MIBC) to identify an optimal definition of pathologic response.

Patients & Methods*:* Patients from 10 international centers who underwent NAC for cT2-4aN0-1 MIBC and achieved <ypT2N0 disease at RC were included. The primary outcome was time to recurrence, either local or distant. Kaplan-Meier and Cox proportional hazards regression were used to evaluate associations between clinicopathologic variables and outcomes.

Results*:* 625 patients were included. Median age was 66 years and 80% were male. Gemcitabine and cisplatin (GC, 56%) and methotrexate, vinblastine, doxorubicin and cisplatin (MVAC)/dose-dense (dd) MVAC (32%) were the most common NAC regimens. ypT0, pure ypTis, ypTa+/-ypTis and ypT1+/-ypTis were attained in 58.1%, 20.0%, 7.6% and 14.2% of patients respectively. The cumulative incidence of recurrence at 5 years was 9%, 16%, 29% and 30% respectively. Pathologic stage was prognostic for recurrence, with ypTa+/-Tis (HR=3.20 [1.40-7.30]) and ypT1+/-Tis disease (HR=4.03 [2.13-7.63]) associated with a significantly higher recurrence risk. Pure ypTis (HR=1.66 [0.82-3.38]) and the type of NAC regimen (ddMVAC: HR=1.59 [0.55-4.56]; MVAC: HR=1.18 [0.25-5.54]; ref: GC) were not associated with recurrence.

Conclusion*:* We propose that optimal pathologic response after NAC be defined as attainment of ypT0N0/ypTisN0 at RC. Patients with ypTaN0 or ypT1N0 disease (with or without Tis) at RC displayed a significantly higher risk of recurrence and may be candidates for trials investigating adjuvant therapy.

INTRODUCTION

Bladder cancer accounts for approximately 3% of all cancers worldwide, with nearly 550,000 cases diagnosed in 2018.(1) Around 25% of patients present with muscle-invasive disease, while up to 20% of patients with non-muscle invasive disease progress to muscle-invasive bladder cancer (MIBC) within 5 years.(2) The recommended management of MIBC is cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) in eligible patients, which has been shown to confer a benefit in overall survival (OS) compared to RC alone.(3-5)

Despite the use of NAC, the long-term prognosis of MIBC is guarded, with around 40% of patients experiencing a disease recurrence after RC.(6, 7) An important prognostic factor is attainment of pathologic response, either pathologic stage ypT0N0 (pathologic complete response, pCR) or <ypT2N0 after NAC. Post-hoc analyses from the SWOG 8710 trial showed a significant improvement in median OS amongst patients who had a pathologic response compared to those who had ≥ypT2N0 disease.(8) However, discrimination of outcomes based on specific pathologic stage <ypT2N0 (i.e. ypTa, ypT1 and ypTis) could not be demonstrated due to modest sample size. Other retrospective analyses have also demonstrated the robust prognostic impact of pCR or <ypT2N0 disease after cisplatin-based NAC.(9-11) However, these studies have been unable to determine whether the depth of pathologic response in the subset of patients with <ypT2N0 disease is prognostic.

While it is known that a subset of patients relapse even after attaining a pathologic response, such patients have not been well characterized in the literature. Furthermore, ongoing clinical trials of neoadjuvant therapy are employing variable pathologic response endpoints and the value of discriminating between the different non-muscle invasive stages is unclear. Finally, trials of adjuvant therapy following NAC are currently only accruing patients with ≥ypT2N0 disease, with the current standard-of-care for patients with <ypT2N0 disease – but not a pCR – being observation. Based on these considerations, we initiated a multi-center collaboration to exclusively study outcomes of patients achieving <ypT2N0 disease after NAC followed by RC for MIBC. We sought to characterize this population, identify specific stages associated with higher risk of recurrence, and aimed to refine the optimal pathologic response endpoint after NAC.

PATIENTS & METHODS

Study cohort

After obtaining institutional review board (IRB) approval, we identified patients who received NAC for MIBC at ten tertiary centers across North America, Europe and Asia between 1996-2019. Participating institutions provided deidentified patient data in accordance with Health Insurance Portability and Accountability Act guidelines.

All patients had a diagnosis of MIBC with a component of urothelial carcinoma histology and underwent NAC prior to RC, and did not receive any adjuvant therapies. RC and lymph node dissection was performed according to local practice by a urologic surgeon at each institution. The key inclusion criteria were the presence of cT2-4a N0-1 at diagnosis of MIBC and achievement of <ypT2N0 disease at RC. N1 patients were included since these patients have been included in some prior trials of NAC(12) and are often treated with NAC in routine clinical practice. Patients who had pure non-urothelial histology were excluded. All patients represented a consecutive cohort of eligible patients treated at each institution and were treated at high-volume tertiary

centers by genitourinary cancer specialists. Treatment decisions and follow-up were according to physician preference based on standards of care at the time. Pathology at RC was reviewed by expert genitourinary pathologists at each center. Clinicopathologic variables collected included the type of NAC, number of cycles of NAC, time between diagnosis and start of NAC, time between end of NAC and RC, and pathologic stage at RC.

Outcomes

The primary outcome was time to recurrence (TTR), either local or distant, whichever occurred first. A second primary tumor within the urinary tract was considered a local recurrence. Death with no prior recurrence was considered a competing risk. The key secondary outcome was OS, defined as duration from RC to death from any cause. Patients without a recurrence or death event were censored at last follow-up where they were confirmed to be alive.

Statistical analysis

Descriptive statistics were used to summarize the patient and tumor characteristics, as well as the outcomes of interest. The Kaplan-Meier method was used to estimate overall survival and recurrence-free survival, while cumulative incidence methods were used to estimate time to recurrence. Cox proportional hazards regression and competing risk methods were used to evaluate factors prognostic for TTR and OS. A multivariable model was constructed using all covariates to explore whether factors were prognostic for TTR. Statistical significance was defined at the α=0.05 level and all tests and confidence intervals were two-sided.

RESULTS

Patient characteristics

A total of 625 patients were included (Table 1). Median age at the time of RC was 66 years and 80% of patients were men. Most patients had pure urothelial histology (n=453, 73%) and had cT2N0 stage at diagnosis (n=449, 72%); 45 patients (7%) had cN1 stage. The median number of cycles of NAC delivered was 4 and the most common NAC regimens used were gemcitabine and cisplatin (GC, n=347, 55.5%) or methotrexate, vinblastine, doxorubicin and cisplatin (MVAC, n=198, 31.7%), administered in either a dose-dense (dd, n=151, 24.2%) or conventional (n=47, 7.5%) manner; 30 patients (4.8%) received split-dose GC and 50 (8%) received a non-cisplatin-based regimen. At RC, 363 patients (58.1%) had ypT0N0 disease, 125 (20%) had pure ypTisN0, 48 (8%) had ypTa +/- TisN0, and 89 (14%) had ypT1 +/- TisN0.

Outcomes after RC

Over a median follow-up of 2.6 years (IQR 1.1-4.6) and maximum of 19.9 years, a total of 76 patients died (12.2%) and 60 patients (9.6%) recurred. Median OS was 14.5 years (95% CI 14.0-not reached) and median TTR was not reached. Among the 60 patients who recurred, median time to recurrence was 1.2 years (range 0.1-8.6). Most recurrences (n=52, 87%) were metastatic, typically occurring in non-liver visceral organs, soft tissue or lymph nodes, while the remaining were local recurrences in the urinary tract, which may also be termed second primaries (Table 2). The cumulative incidence of recurrence at 2 and 5 years was 8.7% (95% CI 6.5-11.6) and 12.6% (9.6-16.6) respectively.

Predictors of recurrence after RC

Table 3 shows the results of uni- and multivariable analyses of clinicopathologic predictors of TTR. On univariable analysis, the only factor associated with TTR was pathologic stage at RC, with ypTa +/- Tis (HR=3.46 [1.54-7.79]) and ypT1 +/- Tis disease (HR=3.96 [2.12-7.39]) conferring a significantly higher risk of recurrence compared to ypT0 disease; pure ypTis was not associated with an increased risk of recurrence (HR=1.66 [0.82-3.35]). This was confirmed in a multivariable model, with ypTa +/- Tis (HR=3.20 [1.40-7.30]) and ypT1 +/- Tis (HR=4.03 [2.13-7.63] being independent predictors of TTR, while pure ypTis (HR=1.66 [0.82-3.38]) was not significantly associated with TTR. Time between diagnosis and NAC and from NAC to RC were not included in the multivariable model as data were missing from >3% of patients for these variables.

On univariable analysis, no other variables, including clinical stage at diagnosis (T3-T4N0: HR=0.78 [0.40-1.51]; $T_{any}N1$: HR=1.35 [0.58-3.18], p=0.54) and the type of NAC administered (ddMVAC: HR=0.72 [0.38-1.38]; MVAC: HR=0.80 [0.31-2.05]; split-dose GC: HR=0.32 [0.04-2.36]); non-cisplatin-based: HR=0.56 [0.20-1.58]; ref: GC; p=0.56) were predictors of TTR.

Outcomes stratified by pathologic stage at RC

Figure 1 shows the cumulative incidence of recurrence up to 5 years after RC, stratified by pathologic stage at RC. The 2- and 5-year probabilities of recurrence were 6% (95% CI 3-10) and 9% (6-13) for ypT0, 6% (3-12) and 16% (9-29) for ypTis, 17% (8-33) and 29% (14-52) for ypTa +/- Tis, and 19% (11-30) and 30% (20-45) for ypT1 +/- Tis respectively.

There were significant differences in OS based on the depth of pathologic response at RC, with 5-year OS of 89% (95% CI 84-92) for ypT0, 84% (71-92) for ypTis, 76% (51-90) for ypTa +/- Tis, and 66% (50-79) for ypT1 +/- Tis (p=0.023, Figure 2).

DISCUSSION

To our knowledge, this is the largest study evaluating the magnitude, nature and predictors of recurrence after achievement of a pathologic response (<ypT2N0) in patients receiving NAC for localized MIBC. In this global, multi-center dataset comprising 625 patients with <ypT2N0 disease at RC, we noted that 9.6% of patients recurred and that recurrences were predominantly at metastatic sites outside the urinary tract. Furthermore, the depth of pathologic response was the only predictor of recurrence, with a significantly higher risk of recurrence seen in patients with ypTa or ypT1 disease (with or without concomitant Tis) at RC, while no difference in outcomes were seen between those achieving pure ypTis or a pCR (ypT0). We therefore propose that attainment of either ypT0N0 or ypTisN0 be used to define optimal pathologic response after NAC.

There are several important implications of our findings. First, we observed a fairly notable risk of recurrence amongst patients not achieving a pCR and in particular, those

with ypTa or ypT1 disease (with or without ypTis). This also translated into an OS difference based on the depth of pathologic response, with a lower OS observed in patients with ypTa/T1 disease compared to those with ypT0/Tis. Since patients with ypTa/T1 disease (with or without ypTis) had a ~30% risk of recurrence, it is worth considering whether such patients ought to be included in trials of adjuvant therapy as only those with muscle-invasive disease after NAC are included in ongoing trials of adjuvant immune checkpoint or FGFR inhibitors.(13)

Second, our results suggest that it may be possible to tailor follow-up after RC based on the depth of response seen at RC. Current guidelines and recommend cross-sectional imaging every 6 months until year 3 after RC before reverting to annual scans until year 5, and then annual renal ultrasonography from years 5 to 10.(2) Given the extremely low risk of recurrence (particularly after 2 years) in patients with ypT0 or ypTis at RC, studies exploring potential de-intensification of surveillance imaging for such patients could be considered.

One of our key findings was that recurrence was seen in a small number (6%) of patients who had a pCR after NAC, with the majority of these (21 of 22) occurring outside the urinary tract. This implies the presence of chemotherapy-resistant micrometastatic disease even when no residual tumor was present in the bladder on routine histologic assessment and underscores the need for further study into the genomic basis of tumors in such patients. Prior work has highlighted that defects in DNA damage response genes, including *ERCC2*,(14) *ATM*, *Rb* and *FANCC*,(15) are associated with response to cisplatin-based NAC and it is possible that patients who recurred despite achievement of a pathologic response after NAC may harbor a lower frequency of alterations in that pathway. Another explanation may be that these patients have a p53-like genomic signature(16) with lower chemosensitivity, particularly in their micrometastatic subclones. Multiregional genomic and immunologic interrogation of these tumors could also potentially enable biomarker-directed selection of patients for adjuvant therapies targeting clonal drivers as well as paving the way towards an individualized approach to surveillance imaging.

We also noted that the specific NAC regimen was not a predictor of recurrence in our selected patient cohort (i.e. those who had achieved a pathologic response to NAC), with no significant differences in TTR between patients receiving GC, conventional MVAC and ddMVAC. Although prospective data only support the use of neoadjuvant MVAC (given every 28 days), GC is frequently used in the neoadjuvant setting in clinical practice, with retrospective analyses suggesting that the pCR rate yielded by GC and MVAC are comparable.(10, 17-21) Administration of MVAC in a dose-dense manner (ddMVAC) with growth factor support every 14 days has also been evaluated as a NAC regimen in single-arm phase 2 trials, with similar rates of pCR to those seen with MVAC.(12) While the rates of pCR appear similar between ddMVAC and GC based on preliminary data from ongoing randomized trials comparing these regimens,(22, 23) some retrospective data have suggested that ddMVAC may be associated with improved OS compared to GC.(24-26) However, our data suggest that if a pathologic response is achieved, subsequent recurrence risk is independent of whether a patient received GC or ddMVAC.

Aside from the inherent drawbacks of a retrospective cohort study, specific limitations of our study include a relatively small event rate (as expected) and lack of centralized radiology and pathology review. The extent and completeness of initial TURBT and its influence on pathologic outcomes was not captured in our database. Some variability in follow-up strategies and radiographic imaging after RC may also exist, although institutions participating in our analysis are recognized cancer centers of excellence; moreover, recurrent disease generally represents aggressive disease that declares itself clinically. Inclusion of patients from academic tertiary centers may have imposed a referral bias, while variability in subsequent salvage therapies at recurrence may have affected survival, although this is not expected to impact TTR, our primary endpoint. Median follow-up in the entire cohort was only 2.6 years, with a relatively small number of patients with follow-up beyond 5 years. Additionally, we did not evaluate the type of surgery (open vs. robotic) nor the extent of pelvic lymph node dissection in our analyses; however all patients were treated at major academic centers by urologic oncologists, and randomized data suggest similar cancer-related outcomes between open and robotic RC(27), and between standard and extended lymph node

dissection.(28) Finally, results of regression models are hypothesis-generating and validation using an external cohort is required.

Nevertheless, this is the largest study assessing outcomes after the achievement of a pathologic response. Importantly, we were able to tease out differences in outcomes between ypTis, ypTa and ypT1 disease and highlight the different phenotype seen with ypTa/T1 (with or without Tis) compared to ypTis, which was not feasible in a prior, smaller study that evaluated 464 patients with <ypT2N0 disease.(11) Moreover, we treated death in the absence of recurrence as a competing risk in recurrence analyses, which ensured that we were specifically able to evaluate cancer-related outcomes in a generally elderly population where OS differences may be hard to discern due to deaths from non-cancer related causes. Finally, this was a large and multinational cohort, which improves the generalizability and validity of our findings.

In summary, our analysis of 625 patients treated at ten major centers identified that 9.6% of patients who achieved a pathologic response (<ypT2N0) after NAC subsequently recurred, predominantly at distant sites. The depth of pathologic response was an independent predictor of recurrence, with a higher recurrence risk seen in patients with ypTa/T1 (with or without Tis) disease and similar outcomes seen amongst patients with ypT0 or ypTis disease. While these findings are hypothesis-generating and require external validation, they may have implications for the selection of the optimal pathologic endpoint in trials of NAC, counselling patients after RC to potentially enable de-intensification of follow-up, and providing a rationale for the evaluation of adjuvant therapy in clinical trials with patients with ypTa/T1 (with or without Tis) disease after NAC. Finally, given the increasing use of immune checkpoint inhibitors in MIBC, the optimal pathologic response endpoint with neoadjuvant immunotherapy and chemo-immunotherapy remains to be determined and further studies evaluating this are needed.(29, 30)

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FIGURE LEGENDS

Figure 1 – Cumulative probability of recurrence in the first 5 years after radical cystectomy, stratified by pathologic stage.

Figure 2 – Overall survival in the first 5 years after radical cystectomy, stratified by pathologic stage.

Table 1 – Baseline characteristics of the cohort.

Characteristic	*N (%)*
Median age (range), years	66 (31-86)
Male gender	499 (80)
Histology	
Pure UC	453 (73)
Mixed* – UC predominant	144 (23)
Mixed˜ – non-UC predominant	28 (5)
Clinical stage at diagnosis	
T2N0	449 (72)
T3-4N0	131 (21)
$T_{any}N1$	45 (7)
Weeks between diagnosis and start of NAC, median (range)^	6 (1-59)
NAC	
GC	347 (56)
ddMVAC	151 (24)
MVAC	47 (8)
Split-dose GC	30 (5)
Non-cisplatin based#	50 (8)
Median number of cycles of NAC (range)˜	4 (1-7)
Weeks between end of NAC and RC, median (range)+	6 (2-25)
Pathologic stage at RC	
ypT0N0	363 (58)
ypTisN0	125 (20)
ypTa +/- TisN0	48 (8)
ypT1 +/- TisN0	89 (14)

* variant histologies included squamous (n=61), adenocarcinoma (n=9), sarcomatoid (n=9), and other (n=65)

˜ variant histologies included squamous (n=9), sarcomatoid (n=4) and other (n=15)

[#] gemcitabine and carboplatin +/- nab-paclitaxel

Data was available for all 625 patients except for the following variables: ^ n=604; ˜ n=622; [+] n=606

Abbreviations: UC – urothelial carcinoma; NAC – neoadjuvant chemotherapy; GC – gemcitabine and cisplatin; dd – dose-dense; MVAC – methotrexate, vinblastine, doxorubicin and cisplatin; RC – radical cystectomy.

Table 2 – Characteristics of the 60 patients who recurred after achieving <ypT2N0 disease at radical cystectomy.

	N (%)
Location of recurrence	
Local (within urinary tract)	8 (13)
Distant (outside urinary tract)	52 (87)
Sites of distant recurrence	
Liver +/- other	9 (17)
Non-liver viscera +/- soft tissue/lymph node	25 (48)
Soft tissue/lymph node only	18 (35)
Clinical stage at diagnosis*	
T2N0	43 (10)
T3-4N0	11 (8)
$T_{any}N1$	6 (13)
NAC regimen*	
GC	38 (11)
ddMVAC	12 (8)
MVAC	5 (11)
Split-dose GC	1 (3)
Non-cisplatin based	4 (8)
Pathologic stage at RC*	
ypT0N0	22 (6)
ypTisN0	12 (10)
ypTa +/- TisN0	8 (17)
ypT1 +/- TisN0	18 (20)

*percentages refer to proportion of patients within that subgroup who recurred

Abbreviations: RC – radical cystectomy; GC – gemcitabine and cisplatin; dd – dose-dense; MVAC – methotrexate, vinblastine, doxorubicin and cisplatin.

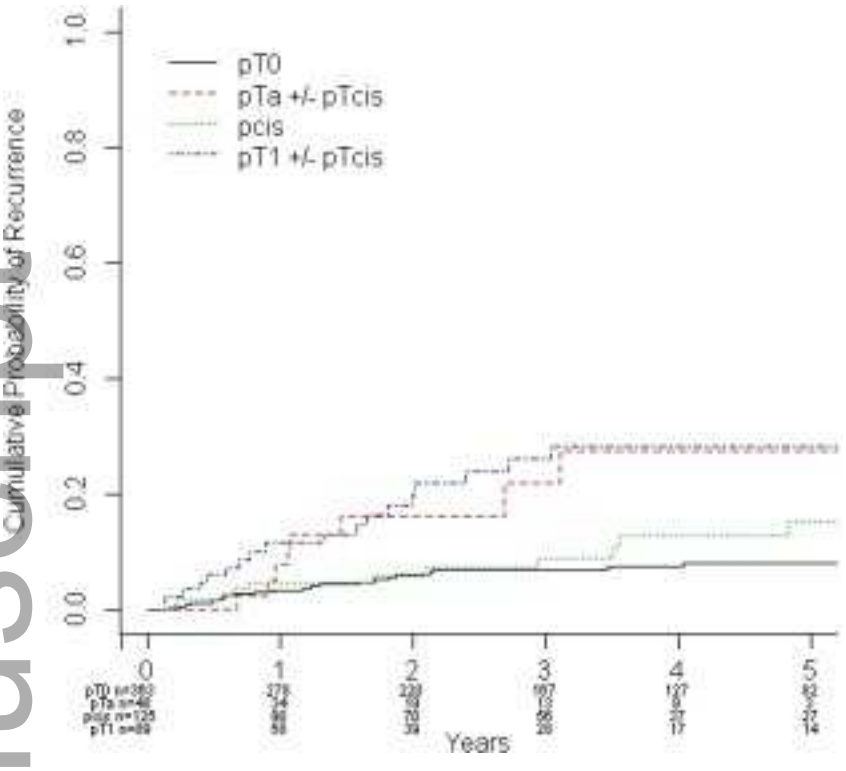
Table 3 – Uni- and multivariable analyses of predictors of TTR.

	Univariable		Multivariable	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*
Age	1.01 (0.99-1.04)	0.31	1.02 (0.99-1.05)	0.14
Female gender (ref: male)	0.68 (0.39-1.20)	0.18	0.59 (0.34-1.05)	0.07
Mixed urothelial histology (ref: pure UC)	1.24 (0.68-2.26)	0.48	1.17 (0.64-2.14)	0.61
Clinical stage at diagnosis (ref: T2N0)		0.54		0.75
T3-T4N0	0.78 (0.40-1.51)		0.81 (0.41-1.58)	
$T_{any}N1$	1.35 (0.58-3.18)		1.16 (0.47-2.86)	
≥6 weeks between diagnosis and start of NAC (ref: <6 weeks)*	1.35 (0.79-2.27)	0.27	-	-
NAC (ref: GC)		0.56		0.51
ddMVAC	0.72 (0.38-1.38)		1.59 (0.55-4.56)	
MVAC	0.80 (0.31-2.05)		1.18 (0.25-5.54)	
Split-dose GC	0.32 (0.04-2.36)		1.15 (0.36-3.69)	
Non-cisplatin-based	0.56 (0.20-1.58)		0.37 (0.04-3.37)	
Number of cycles of NAC	1.24 (0.93-1.64)	0.14	1.17 (0.86-1.59)	0.32
≥6 weeks between end of NAC and RC (ref: <6 weeks)*	0.63 (0.35-1.12)	0.12	-	-
Pathologic stage at RC (ref: ypT0)		**<0.001**		**<0.001**
ypTis	1.66 (0.82-3.35)		1.66 (0.82-3.38)	
ypTa +/- ypTis	3.46 (1.54-7.79)		3.20 (1.40-7.30)	

ypT1 +/- ypTis	3.96 (2.12-7.39)		4.03 (2.13-7.63)	

* These variables were not included in the multivariate model as they had >3% of patients with missing data.

Abbreviations: Ref – referent; HR – hazard ratio; UC – urothelial carcinoma; NAC – neoadjuvant chemotherapy; GC – gemcitabine and cisplatin; dd – dose-dense; MVAC – methotrexate, vinblastine, doxorubicin and cisplatin; RC – radical cystectomy.



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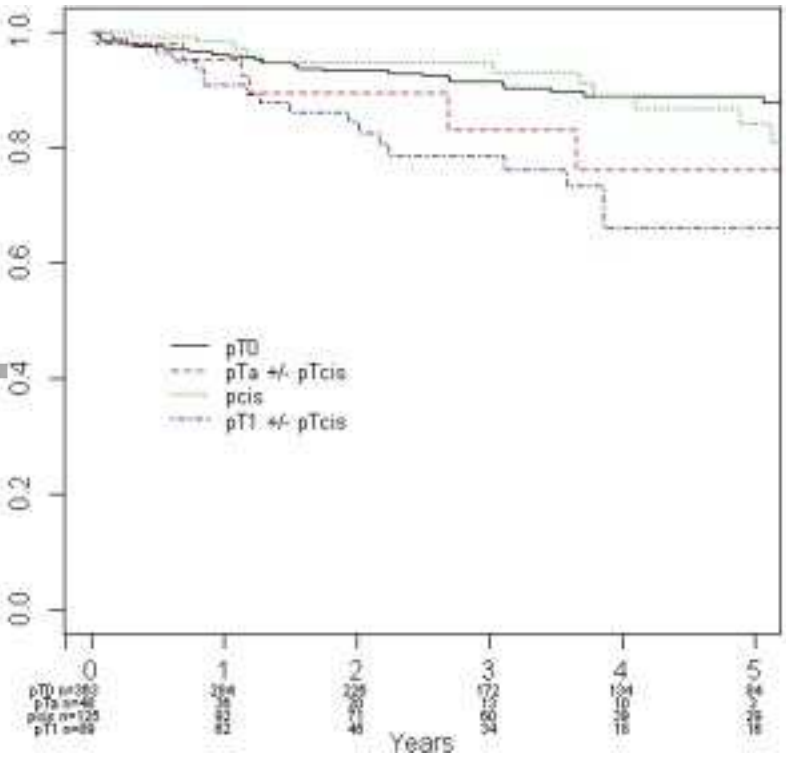

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