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TREATMENT DELAY AND PROGNOSIS IN INVASIVE BLADDER CANCER

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ABSTRACT

Purpose: We studied treatment delay, and the impact on disease specific survival and stage progression in a series of patients who had undergone cystectomy.

Materials and Methods: All 141 patients underwent radical cystectomy between 1990 and 1997 due to locally advanced bladder cancer. Treatment delay was defined as time from pathological confirmation of invasive disease to performance of cystectomy, and was registered retrospectively from the patient charts. Two patients received neoadjuvant chemotherapy and were excluded from further analyses. Followup continued until April 2003 with death due to bladder cancer as the end point. Causes of death were retrieved from the Swedish Cause of Death Registry.

Results: The median treatment delay was 49 days, but was significantly longer for the 71 cases who were referred from other hospitals (63 vs 41 days, $p < 0.001$). Treatment delay did not influence cumulative incidence of death from bladder cancer. Considering all cases, there was no significant correlation between treatment delay and stage progression. For clinical stage T2 tumors, median treatment delay was 76 days among patients with stage progression compared to 41 and 48 days for those with stage regression and stage equivalence, respectively ($p = 0.20$).

Conclusions: Treatment delay was not found to influence disease specific survival in the present study. Furthermore, treatment delay was not significantly longer in cases that progressed compared to those with equal or lower pathological stage in the cystectomy specimen.

KEY WORDS: bladder neoplasms, disease progression, therapeutics, appointments and schedules

Striving for early diagnosis and treatment of malignant tumors is the sine qua non in oncology, and the ultimate goals are to increase the chances of achieving cures and to decrease worry and anxiety. This is no doubt particularly important in cases of invasive tumors. However, diagnosis and treatment are often delayed in uro-oncology as in many other areas of medicine. Studies of bladder cancer have reported a median diagnostic delay (ie time from first symptom to diagnosis) in the range of 105 to 144 days which can be ascribed primarily to health care routines.[1–3] Treatment delay (ie time from diagnosis to treatment with cystectomy or radiotherapy) is also largely due to hospital routines, and median delays of 42 to 63 days have been reported.[4–8]

Muscle invasion in bladder cancer has been characterized "as a major signal of an impending lethal event."[9] Even in cases in which there is only early invasion, as in T1 disease, delayed treatment with radical cystectomy might reduce survival.[10,11] Three current publications suggest that a long interval between diagnosis of invasiveness and performance of cystectomy influences pathological tumor stage[6] and probably also disease specific survival.[5–7] Such reports are alarming because they suggest that slow hospital routines influence patient prognosis. If these results are confirmed, reallocation of resources and changes in hospital practices should be strongly considered. Therefore, we investigated the effects of treatment delay on cancer specific survival and on stage migration from the time of diagnosis of invasive bladder cancer to the performance of radical cystectomy in a well-defined series of hospital cases.

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Nothing to disclose.
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***Editor's Note*: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2074 and 2075.**

MATERIALS AND METHODS

In all 141 patients with locally advanced bladder cancer underwent radical cystectomy between 1990 and 1997 at the Department of Urology of Lund University Hospital. Lymphadenectomy was limited to the obturator fossa, and in 18 patients lymphadenectomy was omitted according to individual surgeon preferences (9 of these 18 patients were thought to have organ confined disease, ie clinical stage T2 or less). A total of 46 patients with locally advanced tumors received preoperative radiation of 20 Gy for 1 week immediately before surgery. The criteria for preoperative radiation were T3 (palpable after transurethral resection) or T4a tumors, however some nonpalpable tumors (11 stage T2 or less) were also selected based on tumor size and surgeon preference. Two patients with clinical stage T4b (TNM 2002) were given 4 courses of neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin. Treatment delay was defined as the interval between the pathology report confirming invasive disease and performance of cystectomy, and was ascertained retrospectively from the charts. Thus, for those patients who received preoperative radiation the week before surgery, this time was included in treatment delay. The 2 patients who obtained neoadjuvant chemotherapy were excluded from study since this therapy increased treatment delay by 16 weeks at the same time as it reduced the tumor. Reasons for treatment delay were also retrieved from the charts. Followup ended in April 2003. Death from bladder cancer was the primary end point, causes of death were obtained from the Swedish Cause of Death Registry until December 2000, and after that further followup information was retrieved from clinical records until April 2003. Those records also substantiated data from the Cause of Death Registry.

Comparisons of treatment delay in groups determined by referral status and by stage progression were done using Wilcoxon's rank sum test and a nonparametric rank based trend test, respectively. The relative hazard of death from bladder cancer was determined by Cox regression analysis. Survival was calculated from the date of diagnosis, but patient followup time was not included in the analysis until the date of cystectomy ("delayed entry")[12] since this event was a prerequisite study inclusion. The main purpose was to analyze the effect of treatment delay. This factor was dichotomized at 60 days, a point that is close to the median in this study and may represent a clinically relevant limit that should not be exceeded. The analysis was also adjusted for potentially confounding factors such as clinical stage, age, sex, preoperative radiation and cases referred from other hospitals. Cumulative incidence curves were used to illustrate the risk of dying of bladder cancer.[12] Time was then calculated from cystectomy and death due to other causes was considered a competing event. The statistical program STATA® version 8.2 was used in all analyses.

RESULTS

Median patient age at surgery was 66 years (range 26 to 82), 116 of the 139 subjects (83%) were men and half of the patients (71) were referred from other hospitals. After the pathology report confirming muscle invasive bladder cancer, 129 of 139 patients were sent for further diagnostic evaluation such as computerized tomography of the abdomen, chest x-ray, urography, renal clearance and split function test. Preoperative radiation was given to 46 patients selected due to locally advanced disease. Of the cystectomies 108 (78%) were performed for muscle invasive disease (clinical stage T2a or higher, tables 1 and 2).

Of the 122 patients 25 (20%) who underwent regional lymphadenectomy had lymph node positive disease. The types of urinary reconstructions performed were ileal conduit in 52 patients (37%), continent cutaneous diversion in 44 (32%) and orthotopic neobladder in 43 (31%). The pathological stage distribution in the patients is shown in table 3.

Median treatment delay was 49 days. It was significantly longer for the 71 patients who were referred from other hospitals (63 days vs 41 days for nonreferred patients, $p < 0.001$). In patients who received preoperative radiation, median treatment delay was 48 days compared to 53 days for patients not given radiation ($p = 0.28$).

Stage migration from clinical tumor stage to pathological tumor stage in cystectomy specimens and treatment delay according to clinical stage are presented in tables 2 and 4, respectively. Considering all patients there was no significant correlation between treatment delay and stage progression (table 5), and median treatment delay was approximately 50 days regardless of stage progression status. The patients with clinical stage T2 tumors are of special interest because such lesions are presumably still confined to the bladder wall. Median treatment delay was 76 days among patients showing stage progression compared to 41 days for those with stage regression. The delay was 48 days for those with stage equivalence (table 6) but this difference was not statistically significant ($p = 0.20$). No difference in treatment delay ($p = 0.49$) was found between patients with and without lymph node metastases.

During followup 84 patients died, 56 of whom due to bladder cancer. Median treatment delay was 48 days (range 20 to 201) among those alive at the end of followup, 52 days (range 0 to 424) among those who died due to bladder cancer and 53 days (range 13 to 1,258) among patients who died of other causes. The incidence of death from bladder cancer was strongly related to pathological stage as shown in figure 1 (trend test $p < 0.001$). Univariate analysis demonstrated that the likelihood of dying of that disease was not affected by other potential risk factors such as sex, age, noncontinent versus continent urinary tract reconstruction, preoperative radiation, or referral versus nonreferral (table 7). Nor was the risk of death from bladder cancer increased in 24 cases of a superficial tumor progressing to muscle invasive disease compared with 84 de novo muscle invasive cases (relative risk [RR] 0.88, 95% CI 0.43 to 1.79, $p = 0.72$). Treatment delay did not influence the incidence of death from bladder cancer (fig. 2 and table 7). For instance, the cumulative incidence of death from bladder cancer was 0.39 (95% CI 0.29 to 0.49) at 5 years for those with a treatment of 60 days or less and 0.36 (95% CI 0.23 to 0.49) for those with a treatment delay greater than 60 days. Nor was the RR changed in multivariate analysis when adjusting for the potential risk factors known at diagnosis (RR 1.02, 95% CI 0.56 to 1.87, $p = 0.94$). We did not adjust for pathological stage because that variable might also depend on treatment delay and, thus, mediate a potential negative impact on the analysis. Some investigators have chosen to group patients according to treatment delay shorter or longer than 3 months but this cutoff had no effect on the results of our analysis. The RR was 0.76 (95% CI 0.37 to 1.56) comparing patients with treatment delay greater than 90 days versus 90 days or less in a univariate analysis and 0.72 (95% CI 0.35 to 1.51) in a multivariate analysis adjusting for factors known at diagnosis.

DISCUSSION

The median treatment delay in our study was 49 days, which is comparable to data from the United Kingdom concerning patients with a median treatment delay of 9 weeks from transurethral resection of the bladder to definitive treatment with radiotherapy or radical cystectomy.[8] In our series of patients as in 2 other series[6,8] the results of the analyses indicated that a long treatment delay had no influence on disease specific survival. Wallace and Harris were the first to suggest that treatment delay may result in a worse prognosis,[13] and thus far that conclusion has only been confirmed by Sanchez-Ortiz[5] and May et al.[7] The latter investigators compared patients with short and long treatment delays, but those 2 groups comprised different proportions of extravesical disease (48% and 84%, respectively). Consequently some authors believe that there is not yet sufficient evidence to suggest that early treatment will translate into improved survival.[14] All studies that have concerned treatment delay and prognosis, including the present investigation, have been rather small and hence have only had the

TABLE 1. *Baseline characteristics of the study group*

	No. Pts	Treatment Delay 60 Days or Less	Treatment Delay Longer Than 60 Days
Male/female	116/23	71/15	45/8
Age 65 or older/younger than 65	76/63	46/40	30/23
De novo muscle invasive disease/progression to muscle invasion	84/24	52/13	32/11
Noncontinent/continent urinary tract diversion	52/87	26/60	26/27
Preop radiation yes/no	46/93	31/55	15/38
Referred: yes/no	70/69	31/55	39/14

TABLE 2. *Stage migration as change from clinical to pathological stage*

Clinical Stage	Pathological Stage				
	pT1 or Less	pT2	pT3	pT4	Totals
T1 or less	14	6	3	4	27
T2	9	25	14	3	51
T3	3	13	18	6	40
T4	4	2	5	6	17
Missing	0	3	1	0	4
Totals	30	49	41	19	139

TABLE 3. *Distribution of pathological stage and lymph node status*

	No. Pts (%)
Lymph node status:	
Neg	97 (70)
Pos	25 (18)
Unknown	17 (13)
Pathological stage:	
pT0	10
CIS	8
pTa	2
pT1	9
pT2	1
pT2a	19
pT2b	30
pT3a	21
pT3b	20
pT4a	16
pT4b	3

TABLE 4. *Treatment delay according to clinical stage*

Clinical Stage	No. Pts	Median Days Treatment Delay (range)
T1 or less	27	47 (0–335)
T2	51	48 (20–1,258)
T3	40	49 (18–424)
T4	17	71 (15–278)
Missing	4	60 (37–159)

TABLE 5. *Treatment delay and stage migration*

	No. Pts	Median Days Treatment Delay (range)
Stage regression	36	47 (15–293)
Clinical stage = pathological stage	63	51 (18–245)
Stage progression	36	51 (0–1,258)

TABLE 6. *Treatment delay and stage progression of clinical stage T2 tumors*

	No. Pts	Median Days Treatment Delay (range)
Stage regression	9	41 (27–89)
Clinical stage = pathological stage	25	48 (20–170)
Stage progression	17	74 (27–1,258)

Nonparametric trend test p = 0.20.

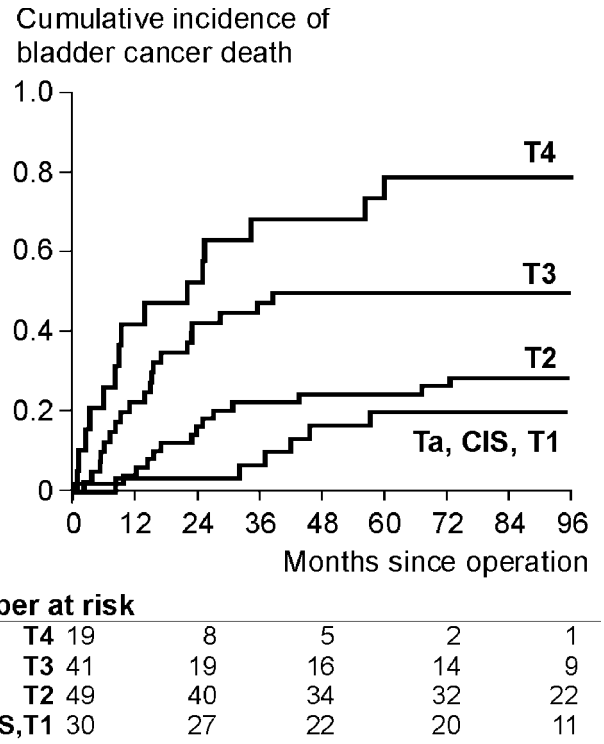

FIG. 1. Pathological stage dependent cumulative incidence of death from bladder cancer.

power to detect strong correlations. In addition to sample size, a relatively short median treatment delay in our study and other similar studies (mean treatment delay 55[5] and 56[7] days, respectively) decreases the power to detect an effect on disease specific survival. Also in those studies it is possible that earlier allocation of more advanced cases to definitive treatment influenced survival in a way that was not corrected for. For example, in our investigation the median treatment delay was slightly shorter for patients who had more advanced tumor stage and were selected for preoperative radiation than for patients who were not given radiation therapy. It cannot be ruled out that within each clinical stage, which was adjusted for, some patients had more advanced lesions such as larger tumors and tumors with more pronounced local symptoms, and were therefore submitted to cystectomy earlier and, thus, had a shorter treatment delay. In such cases, shorter treatment delay would be associated with increased risks of stage progression and death from the disease. It is also plausible that true progression of the malignancy with increased local symptoms can lead to earlier cystectomy and shorter treatment delay, which would also increase the possibility that the cases within each clinical stage that were most advanced at diagnosis in our study were assigned to cystectomy earlier than other cases, thus generating confounding between short treatment delay and advanced tumors within individual clinical stages. This theory could explain why we found that treatment delay was not longer for patients with tumor progression than for patients with cystectomy specimens showing unchanged or lower pathological stage (tables 5 and 6).

In addition to treatment delay, there are several other factors related to medical services, including center experience, that influence the outcome of the treatment of invasive bladder cancer. Hospital volume (number of cases treated annually) and surgeon volume have been found to impact

TABLE 7. *Univariate analysis of risk of death from bladder cancer*

	Hazard Ratio	95% CI	p Value
Female vs male	0.47	(0.20–1.11)	0.085
Age younger than 65 vs 65 yrs or older	1.10	(0.64–1.86)	0.74
De novo muscle invasive vs progressing to muscle invasion	0.88	(0.43–1.79)	0.72
Clinically organ confined tumor (clinical stage T2 or less) vs nonorgan confined	0.88	(0.46–1.66)	0.69
Continent vs noncontinent urinary tract diversion	0.62	(0.36–1.05)	0.076
Preop radiation vs no radiation	0.92	(0.52–1.63)	0.77
Referred cases vs nonreferred cases	0.98	(0.58–1.66)	0.93
Treatment delay greater than 60 vs 60 days or less	1.05	(0.61–1.82)	0.85

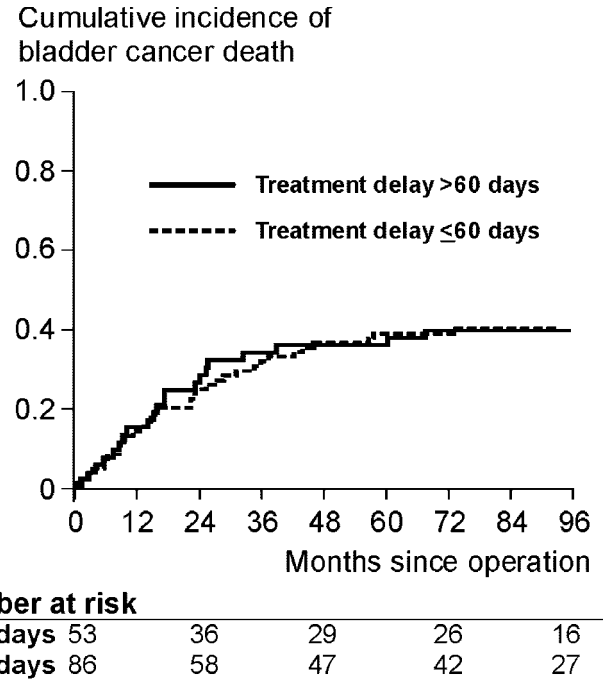

FIG. 2. Cumulative incidence of death from bladder cancer according to treatment delay.

mortality after cystectomy,[15–17] and those factors may also affect treatment delay and bladder cancer mortality, making them potential confounders with uncontrollable effects on the results.

In our study as well as in general, treatment delay can be explained by the need for diagnostic investigations such as computerized tomography of the abdomen, chest x-ray, urography, renal clearance and split function test, and to some extent also by the waiting time for referral and cystectomy. If clinicians were aware of invasive bladder cancer as early as at transurethral biopsy and, in addition, could immediately plan necessary investigations, it might be possible to reduce treatment delay.

Clinical stage and other potentially prognostic factors known at diagnosis were weak prognostic factors for death from bladder cancer (table 7). Moreover, clinical stage T2 and T3 tumors had similar outcomes in our study, possibly because most of the T3 lesions were treated with preoperative radiation or reflect inaccuracy in clinical staging. This observation does not agree with the moderate difference between T2 and T3 tumors as reported by other investigators (75% vs 58% 5-year survival, respectively).[18] Clearly to individualize treatment by selecting patients for neoadjuvant chemotherapy before cystectomy, better prognostic variables are needed.

Prolonged delay of cystectomy may have other effects besides decreasing the chance of survival. Is it ethically acceptable that patients have to wait months for removal of a potentially lethal tumor? Few studies have examined the effects that long periods of waiting for surgery can have on patient health related quality of life. A muscle invasive bladder tumor causing symptoms such as hematuria or urge is likely to have a profound impact on quality of life. In addition, a patient will probably become resentful and blame the health services if advanced disease is found at surgery after a prolonged treatment delay.

CONCLUSIONS

Treatment delay was not found to influence disease specific survival in the patients we studied. Furthermore, treatment delay was not significantly longer for patients who had tumors that progressed compared to those in whom cystectomy specimens showed equal or lower pathological stage. This counterintuitive finding might be explained by bias due to confounding between short treatment delay and more advanced tumors within each clinical stage. In addition, our study was rather small and could therefore only detect strong relationships between treatment delay and prognosis.

REFERENCES

1. Mommsen, S., Aagaard, J. and Sell, A.: Presenting symptoms, treatment delay and survival in bladder cancer. Scand J Urol Nephrol, **17:** 163, 1983
2. Wallace, D. M., Bryan, R. T., Dunn, J. A., Begum, G., Bathers, S. and West Midlands Urological Research Group: Delay and survival in bladder cancer. BJU Int, **89:** 868, 2002
3. Mansson, A., Anderson, H. and Colleen, S.: Time lag to diagnosis of bladder cancer—influence of psychosocial parameters and level of health-care provision. Scand J Urol Nephrol, **27:** 363, 1993
4. Fong, B. C., Miller, D., Mahmud, S., Tanguay, S. and Aprikian, A. G.: Operative delay is an independent predictor of disease recurrence after radical cystectomy. J Urol, suppl., **169:** 339, abstract DP3, 2003
5. Sanchez-Ortiz, R. F., Huang, W. C., Mick, R., Van Arsdalen, K. N., Wein, A. J. and Malkowicz, S. B.: An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol, **169:** 110, 2003
6. Chang, S. S., Hassan, J. M., Cookson, M. S., Wells, N. and Smith, J. A., Jr.: Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. J Urol, **170:** 1085, 2003
7. May, M., Nitzke, T., Helke, C., Vogler, H. and Hoschke, B.: Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. Scand J Urol Nephrol, **38:** 231, 2004
8. Chahal, R., Sundaram, S. K., Iddenden, R., Forman, D. F., Weston, P. M. and Harrison, S. C.: A study of the morbidity, mortality and long-term survival following radical cystectomy and radical radiotherapy in the treatment of invasive bladder cancer in Yorkshire. Eur Urol, **43:** 246, 2003
9. Prout, G. R., Jr., Griffin, P. P. and Shipley, W. U.: Bladder carcinoma as a systemic disease. Cancer, **43:** 2532, 1979
10. Stockle, M., Alken, P., Engelmann, U., Jacobi, G. H., Riedmiller, H. and Hohenfellner, R.: Radical cystectomy—often too late? Eur Urol, **13:** 361, 1987
11. Herr, H. W. and Sogani, P. C.: Does early cystectomy improve

survival of patients with high risk superficial bladder tumors? J Urol, **166:** 1296, 2001
12. Kalbfleisch, J. D. and Prentice, R. L.: The Statistical Analysis of Failure Time Data, 2nd ed. New York: Wiley, 2002
13. Wallace, D. M. and Harris, D. L.: Delay in treating bladder tumours. Lancet, **19:** 332, 1965
14. Chahal, R. and Harrison, S. C. W.: Re: An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma (letter to the editor). J Urol, **170:** 1327, 2003
15. Birkmeyer, J. D., Stukel, T. A., Siewers, A. E., Goodney, P. P., Wennberg, D. E. and Lucas, F. L.: Surgeon volume and operative mortality in the United States. N Engl J Med, **349:** 2117, 2003
16. Birkmeyer, J. D., Siewers, A. E., Finlayson, E. V., Stukel, T. A., Lucas, F. L., Batista, I. et al: Hospital volume and surgical mortality in the United States. N Engl J Med, **346:** 1128, 2002
17. Elting, L. S., Pettaway, C. A., Grossman, H. B., Bekele, B. N., Saldin, K. R. and Dinney, C. P. N.: Relationship between postoperative in-hospital mortality and annual hospital volume of cystectomies: the effect of centers of experience. J Urol, suppl., **169:** 336, abstract 1301, 2003
18. Nishiyama, H., Habuchi, T., Watanabe, J., Teramukai, S., Tada, H., Ono, Y. et al: Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990–2000 in Japan. Eur Urol, **45:** 176, 2004

EDITORIAL COMMENT

"You may delay, but *Time* will not."—Benjamin Franklin

The authors address an important topic which has received increasing attention in the management of invasive bladder cancer. Specifically, does delay in treatment compromise survival? This series contained 141 patients with invasive bladder cancer treated with radical cystectomy during an 8-year period. Treatment delay was defined retrospectively as time from pathology report at diagnosis until cystectomy, and was further divided into doctor and hospital delay. The major conclusion of this study was that treatment delay did not impact stage progression or survival, which is contrary to what has recently been published in several contemporary series. However, the preponderance of evidence to date demonstrates that a delay of greater than 90 days has a significantly negative impact on outcomes including overall survival. Interestingly, in this series the median delay was only 51 days. Thus, while delay might adversely impact overall survival, this particular cohort was treated relatively expeditiously and, thus, the true impact of delay may not be detectable in this study. What cannot be easily measured is the delay that may be present at the time of initial patient presentation. Furthermore, some treatment delay may be unavoidable to safely evaluate the patient in preparation for planned cystectomy. Nevertheless, I think there is a window of curability that can be exceeded. Therefore, once the decision has been made to perform radical cystectomy, it should be performed in a timely fashion, and all efforts should be made to minimize delay where necessary and to avoid needless delay. In other words, you may delay, but *Tumor* will not.

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