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Stereotactic radiotherapy for brain metastases in patients with lung cancer; outcome and toxicity in clinical practice

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ABSTRACT

Background: Stereotactic radiotherapy (SRT) is an established modality for treating limited brain metastases (BMs). This study aimed to assess the real-life treatment outcome and associated prognostic factors for survival in a consecutive lung cancer cohort receiving SRT for BMs.

Materials and methods: A retrospective review and analysis of patients with lung cancer with BMs treated with SRT in western Sweden between 2002 and 2017 were performed. Data were collected from patient charts and the radiotherapy dose planning system.

Results: One hundred nine patients corresponding to 139 lesions were assessed; the majority were treated with single-fractionated SRT with 20 Gy. The median overall survival (OS) was 6.1 months, with a 12-month survival rate of 24%. The estimated overall disease control rate (DCR) was 84% at a median time of three months. On multivariate analysis, WHO performance status (PS) ($p = 0.002$) and smoking status ($p = 0.005$) were significant predictive factors for survival. Four percent of the patients experienced possible grade III–IV toxicity, and previously administered cranial radiation therapy was a significant independent factor ($p = 0.03$) associated with the risk of developing acute toxicity.

Conclusions: SRT due to brain metastases from lung cancer is a well-tolerated treatment. When selecting patients suitable for treatment, PS and extracranial disease progression should be considered. Smoking cessation is probably of value even in this palliative setting. The goal of SRT for BMs is not only to improve survival but also to provide symptom relief, and future studies on SRT should assess patient-reported outcomes in addition to survival.

Key words: stereotactic radiotherapy (SRT); brain metastases; lung cancer

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Introduction

Lung cancer is the leading cause of cancer death worldwide [1] partly due to its inborn aggressiveness and metastatic behavior. Thirty to fifty percent of the patients diagnosed with nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC) will develop brain metastases (BMs) at some stage of their disease [2, 3]. In the presence of BMs, the prognosis is generally poor, but prognostic indicators for survival include age, Karnofsky performance status (KPS), the number of BMs and the presence of extracranial metastases [4]. BMs constitute a huge clinical challenge with a profound impact on quality of life and, considering the historically poor prognosis of the patients, optimized BM-directed treatment is highly warranted.

For decades, whole-brain radiotherapy (WBRT) in combination with steroids has been widely used in the management of patients with brain metas-

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tases [5], while surgical resection has been mainly performed in selected cases, e.g., single metastasis. However, during the last decade, stereotactic radiotherapy (SRT) has become an increasingly utilized treatment option for single BMs and intracranial (IC) oligometastatic disease.

Randomized controlled trials (RCTs) have compared SRT alone to SRT plus WBRT in patients with IC oligometastatic disease, and no survival advantage has been observed with the combination over SRT alone, although distant IC relapse seemed to occur more frequently in patients receiving SRT alone [6–9]. However, adjuvant WBRT may increase the risk of neurocognitive deterioration [9, 10] and negatively affect health-related quality-of-life (HRQL) [11]. Due to these adverse effects as well as the lack of a survival gain of the combined treatment approach, SRT has become the preferred primary treatment in patients with IC oligometastatic disease.

Although the use of SRT as a treatment modality is well established, there is no clear consensus regarding the dose levels or optimal fractionation to be used to obtain local IC disease control while preserving HRQL. A dose-response relationship has been demonstrated where the likelihood of local control twelve months after treatment is higher with increasing SRT doses [12], but the toxicity was also correlated with increased doses. Additionally, the side effects increase with larger irradiated volumes [13,14], and a treatment option for large lesions or lesions located near organs at risk (OAR) is to administer hypofractionated SRT (HFSRT) instead of a single fraction. Local control twelve months after HFSRT has been reported to be comparable to that of SRT [15,16], with a lower grade of toxicity [17].

At our institution, BMs have been treated with SRT for nearly two decades. In this study, we aimed to assess a consecutive lung cancer cohort regarding treatment practices, clinical outcomes and possible associated prognostic factors for survival.

Materials and methods

Study design

We conducted a retrospective study of patients treated with cranial SRT due to BMs from primary lung cancer at the Sahlgrenska University Hospital in Gothenburg between 2002 and 2017, and approval to conduct this study was granted by the Regional Ethical Review Board in Gothenburg, Sweden. The main objective was to determine the local control rate and overall survival and identify clinical- and radiotherapy-related parameters impacting the survival rates and/or local control. Another objective was to rate and grade treatment-related toxicity and identify potential correlations with the tumor size and brain irradiation dose.

Consecutive patients who were diagnosed with primary lung cancer (either NSCLC or SCLC) and had received radiotherapy due to brain metastases with SRT or HFSRT included. In general, patients were considered suitable for treatment if they had a WHO performance status (PS) of 0–2, a limited number of metastases (1–3 lesions) and a tumor diameter not exceeding 3.5–4 cm. The patients were identified using the Oncology Information System at the radiotherapy department, the patient and tumor data were collected from patient charts, and the dosimetric data were extracted from the radiotherapy administrative system. The data included age, smoking status (a former smoker was defined as having quit smoking > 1 year ago), PS, tumor histology, extracranial (EC) disease status at the time of SRT (categorized according to the number of organs with metastatic disease and whether the EC disease was in remission/stable, progressive, not detectable or newly diagnosed—i.e., never treated), the number of BMs and the lines of therapy. Treatment-related data, such as the dose-volume data, volume of the brain receiving > 12 Gy (V_{12}), toxicity, local control of treated lesions or new BMs, additional or previous cranial radiotherapy and EC progression, were also extracted. Treatment-related toxicities that occurred < 6 months after SRT treatment were compiled and assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. Local control, local failure or distance intracranial progression were assessed from magnetic resonance imaging (MRI) or computer tomography (CT) scans after SRT treatment.

Treatment procedure

The patients were immobilized using a thermoplastic stereotactic head mask and were subjected to a CT scan performed in the treatment position. From 2015 and thereafter, MRI was performed in the treatment position. However, for most of

the patients, MRI was performed pretherapeutically and then the images were fused with the CT images. The gross target volume (GTV) and organs at risk were delineated on the fused CT/MRI images, and the planning target volume (PTV) was generated by adding a margin of 2–3 mm. During the study period, the dose was prescribed with 100% in the isocenter, and 90% of the prescribed dose should cover the PTV. All the tumors were treated with linear accelerator-based SRT using 5–6 dynamic arcs to deliver 6-MV photon beams. The number of fractions and total dose prescribed for each SRT treatment varied depending on the tumor volume, location of BM relative to OAR and whether a patient had received previous cranial radiotherapy (i.e., WBRT or partial radiotherapy). However, typically, single-fraction treatment would be administered with 18–20 Gy and HFSRT with 7–10 Gy per fraction.

Statistical analysis

The outcome data with local control and toxicity were presented descriptively, where potential prognostic factors were analyzed by logistic regression. Overall survival was assessed by the Kaplan–Meier method, and possible prognostic factors for survival were calculated by Cox regression.

Results

The screening of patients who had received cranial SRT due to brain metastases from lung cancer resulted in 109 patients who were eligible for further analyses.

Patient, tumor and treatment characteristics

The details of the patient, tumor and treatment-related characteristics are described in Table 1. Of 109 included patients, most were female, the median age was 66 years, 80% were in PS 0–1, and 83% were former or ongoing smokers. At the time of SRT treatment, most of the patients were either classified with newly diagnosed EC disease — i.e., SRT was part of primary treatment (36%) — or had EC disease in control (35%). Fifteen percent had no detectable EC disease, while 14% of the patients had EC disease progression. In total, 69% of the patients had EC metastases at the time of SRT treatment, most commonly, only

Table 1. Patient, tumor and treatment characteristics

Characteristi cs	n (%)
Gender	
Female	65 (60%)
Male	44 (40%)
Age [years]	
Median	66 (41–85)
WHO Performance Status at the time of SRT	
0	30 (28%)
1	56 (51%)
≥ 2	23 (21%)
Smoking status at the time of SRT	
Current smoker	36 (33%)
Former smoker	55 (50%)
Never smoker	13 (12%)
Unknown	5 (5%)
Histology	
Adenocarcinoma	67 (61%)
Squamous cell carcinoma	16 (15%)
NSCLC not classified	8 (7%)
SCLC	16 (15%)
Other	2 (2%)
No. of IC lesions at the time of SRT	
1	79 (70%)
2	27 (24%)
≥ 3	6 (6%)
Additional/Prior cranial RT	
No	65 (60%)
Yes	44 (40%)
Additional cranial SRT	
No	86 (79%)
Yes	23 (21%)
Extracranial disease status at the time of SRT	
In control	38 (35%)
Progressive	15 (14%)
Not detectable	16 (15%)
Newly diagnosed	40 (36%)
No. of extracranial organs with metastatic disease	
Brain alone	34 (31%)
1	42 (39%)
2	19 (17%)
≥ 3	14 (13%)
No. of previous treatment lines	
None	40 (36%)
1–2	53 (49%)
≥ 3	16 (15%)
PTV volume [cm^3]	
Median (range)	5.5 (0.6–25.9)
D2% PTV [Gy]	
Median (range)	20.3 (15–28.8)

Table 1. Patient, tumor and treatment characteristics

Characteristi cs	n (%)
D98% PTV [Gy]	
Median (range)	18.3 (13.4–25.5)
D50% PTV [Gy]	
Median (range)	19.6 (14.7–27.7)
V_{12} (cm^3)	
Median (range)	8.7 (0.8–28.5)
Prescribed dose [Gy]	
Median (range)	20 (15–28)
20 Gy	87 (63%)
18 Gy	31 (22%)
15–17 Gy	12 (9%)
5–10 Gy	9 (6%)
No. of given treatment fractions	
1	129 (93%)
2	7 (5%)
≥ 3	3 (2%)

WHO — World Healt Organization; SRT — stereotactic radiotherapy; RT — radiotherapy; NSCLC — non-small cell lung cancer; SCLC — small cell lung cancer; IC — intracranial; PTV — planning target volume

in one organ (39%). Most of the patients (70%) had one IC lesion, and 24% had two IC metastases. Eighty-one patients (74%) received SRT against one target, and 27 patients (25%) against two targets. In total, 139 IC lesions were treated with SRT in the study population. The irradiated volumes had a median PTV of 5.5 cm^3 (0.6–25.9 cm^3). Most of the metastases (93%) were treated with single-fractionated SRT, and the most commonly prescribed dose was 20 Gy (15–28 Gy).

Toxicity

Treatment-related acute toxicity was evident in six patients and could not be ruled out in additional fifteen patients who presented with neurological deficits < 6 months after SRT treatment (Supplementary File — Tab. S1). Among those 21 patients with apparent or possible toxicity, most (n = 17) had grade I–II adverse events. Three patients developed possible grade III toxicity, and one grade IV IC hemorrhage was observed. In multivariate analyses of potential factors that might be associated with the risk of developing acute toxicity, only previously administered cranial RT (p = 0.03) was statistically significant. No correlation with increased toxicity was observed regarding the age, size of PTV, large $V_{12,}$ or dose per fraction (Supplementary File — Tab. S2).

Local control

Local control was assessed at a median time of three months. Thirty-four patients (corresponding to 42 target lesions) were not eligible for evaluation due to the absence of follow-up brain imaging or missing data regarding MRI/CT scans. Of the 97 evaluable metastases, twelve lesions (12%) showed a complete response on the initial MRI/CT scans after SRT treatment. Another 40 lesions (41%) showed a partial response, and 29 lesions (30%) showed stable disease. Thus, the overall disease control rate (DCR) was 84%; local failure was observed in 16 lesions (16%). Distant IC progression was observed in 28% of the patients (n = 21) at the time of the first MRI/CT scan, whereas 72% of the treated patients (n = 54) had no signs of distant failure. Further data regarding the responses are described in Supplementary File — Table S3.

Multivariate analysis was performed on the single fractionation group to assess whether the PTV volume, delivered dose, smoking or tumor subtype were significant prognostic factors for a response. However, none of the factors were statistically significant.

Survival

At the time of analysis, eight of 109 patients were still alive. The overall median survival after SRT treatment for the entire cohort was 6.1 months. The 12-month survival rate was 24% (Fig. 1). Multivariate analyses performed to investigate potential prognostic factors of survival (Tab. 2) showed that PS (p = 0.002) and smoking status (p = 0.005) were significant factors (Fig. 2), whereas the 12-month survival rate was 53% for patients who had never smoked compared with 25% for former smokers and 11% for on-going smokers. Other potential prognostic factors, such as age, the number of IC lesions at the time of SRT, metastatic burden (i.e. number of EC organs with metastases) and PTV volume failed to achieve statistical significance (Supplementary File — Fig. S1A–D). We also observed no significant difference regarding the EC disease status (in control, progressive, not detectable, newly diagnosed) at the time of SRT (Supplementary File — Fig. S2), although a trend for increased survival in patients with EC disease in control or newly diagnosed patients was observed and a tendency for a worse prognosis in patients with no detectable EC disease. Gender

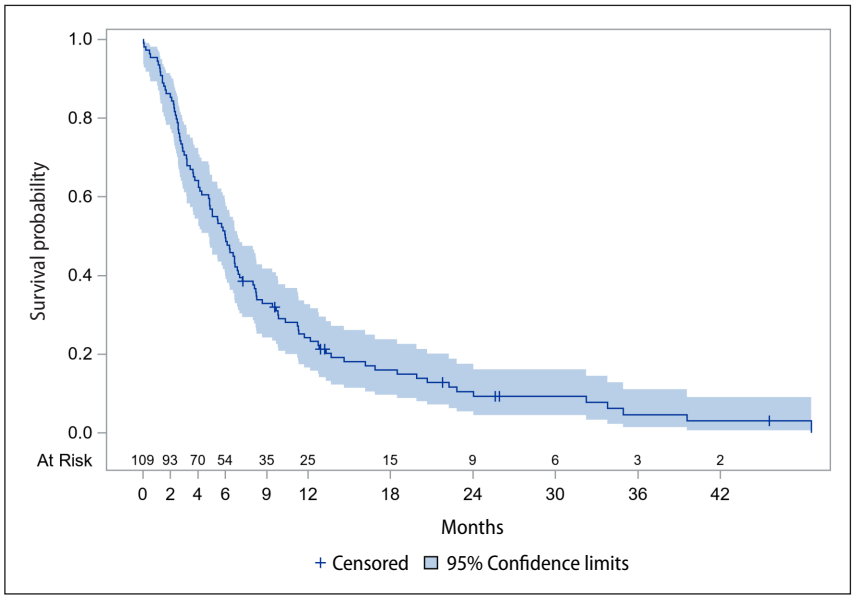

Figure 1. Survival analysis. Overall survival (no patients were excluded)

Table 2. Prognostic variables predicting overall survival

Variable	Univariate analyses Hazard ratio (95% CI)	p (univariate)	Multivariate analyses Hazard ratio (95% CI)	p (multivariate)
Metastatic burden	1.02 (0.84–1.25)	0.830	–	NS
Performance status	1.52 (1.13–2.05)	0.006	1.57 (1.16–2.12)	0.002
Subtype	0.52 (0.30–0.91)	0.022	–	NS
Extracranial disease: EC control *vs.* EC progression	2.37 (1.25–4.47)	0.008	–	NS
Extracranial disease: EC control *vs.* newly diagnosed/untreated	1.09 (0.68–1.74)	0.721	–	NS
Extracranial disease: EC control *vs.* no EC detected	1.52 (0.82–2.81)	0.184	–	NS
Age	1.00 (0.98–1.02)	0.889	–	NS
No. of IC metastases	1.27 (0.87–1.87)	0.216	–	NS
Smoking status	1.605 (1.16–2.21)	0.004	1.57 (1.14–2.17)	0.005
PTV group	1.141 (0.89–1.46)	0.300	–	NS
Dose per fraction	0.76 (0.58–1.00)	0.050	–	NS
Gender	1.20 (0.80–1.80)	0.366	–	NS

CI — confidence interval; EC — extracranial; IC — intracranial; PTV — planning target volume

was not a significant factor, although a tendency to increased survival in women was observed (Supplementary File — Fig. S3). The tumor subtype and delivered dose per fraction were found to be significant factors in univariate analysis, where a lower dose and SCLC implied inferior survival, but these results were not significant in the subsequent multivariate analyses (Supplementary File — Fig. S4AB).

Discussion

In this retrospective study, we investigated the clinical outcome and associated prognostic factors in lung cancer patients treated with SRT due to brain metastases. The median OS in this cohort was 6.1 months, with a 12-month survival rate of 24%, which is in the range of the median OS of 4.5–17.1 months reported previously after cranial

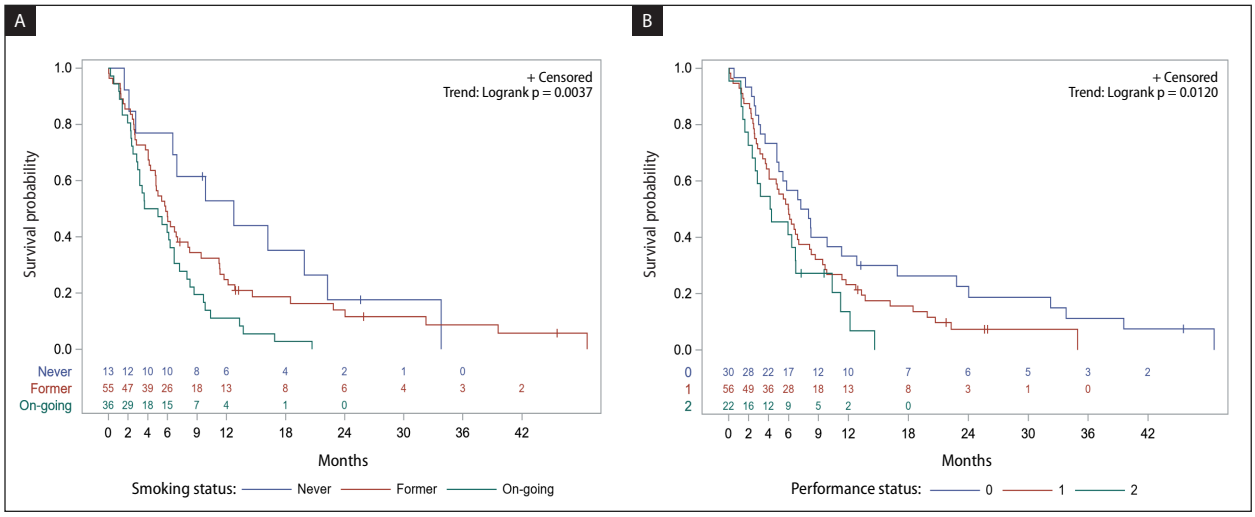

Figure 2. Survival by smoking status (**A**) and by performance status (PS) (**B**). Survival by PS (0–2) and survival by smoking status (excluding 5 patients with unknown smoking status)

SRT in patients with primary lung cancer [6, 8, 16, 18–23]. The rather low median OS in our report may be attributed to the heterogeneous population of consecutive unselected patients and the long period of 15 years. Clinical practice regarding staging has changed dramatically during the period of this study, and substantial progress has been made in systemic treatment with treatable gene alterations impacting prognosis for which patients treated during the early 2000s generally performed worse. The analyses showed that PS ($p = 0.002$) and smoking status ($p = 0.005$) are statistically significant predictors of survival. PS as a prognostic factor for survival in lung cancer patients treated with cranial SRT has been demonstrated in several other studies [18–21]. However, to our knowledge, no previous study has reported the smoking status as a significant predictor of OS. Our results not only indicate superior survival for patients who were never-smokers but also revealed an advantage in patients who stopped smoking at a palliative stage of the disease compared with the group who continued to smoke. Therefore, it may also be important to encourage patients in the palliative stage of their disease course to quit smoking. The never-smoker population likely included a high number of cancers with oncogenetic drivers, but this was not prospectively tested during most of the study period.

In addition to PS, Zindler et al. also showed the presence of extracranial metastases and age to be prognostic factors for survival after SRT for brain metastases of NSCLC [19]. Similar findings were demonstrated by Sperduto et al. [24] and Nieder et al. [25] The latter two also reported that the number of brain metastases was a significant predictor of survival. In our analysis, the number of IC metastases at the time of SRT was not a significant predictor, acknowledging that the number of patients with multiple BMs was very few. The number of IC metastases was also not a significant predictor in the study by Zindler et al. [19] In 2014, Yamamoto et al. investigated whether SRT as upfront treatment for patients with five to ten BMs was noninferior compared with patients with two to four metastases in terms of OS [18]. The patient cohort in this study comprised mostly lung cancer patients, and the authors demonstrated that a solitary brain metastasis was significantly associated with longer survival, but no difference in OS was found between the two patient groups with 2–4 or 5–10 BMs. Another finding was that stable EC disease was a significant predictor for OS, in contrast to the findings reported by Zindler [19]. We also observed no statistically significant survival benefit regarding the EC disease status or EC metastatic burden at the time of SRT. We observed a trend for increased survival in patients with EC disease in control or patients who were treatment naïve compared with those with EC disease in progression. There was also a tendency for patients with no detectable EC disease to have a worse prognosis than those with newly diagnosed disease or EC disease in control. This finding is somewhat counterintuitive but might be related to negative selection,

in part explained by patients who have relapsed despite adjuvant chemotherapy after surgery, signaling a more aggressive disease. Our finding that the EC metastatic burden (measured as the number of metastatic sites) does not impact survival is important, stressing that patients should not be excluded from SRT treatment based on the extent of EC disease. Additionally, age should not per se be an exclusion factor because we found no association with survival or toxicity. No correlation was observed between the size of PTV or delivered dose per fraction and survival in this study. A lower dose implied inferior survival in univariate analysis, although the results were not significant in subsequent multivariate analysis, a finding that agrees with those of Abraham et al. [27]. A tendency existed toward inferior survival for patients with SCLC histology in univariate analysis, possibly indicating a poorer treatment effect of cranial SRT in SCLC patients. One explanation might be the high probability of CNS dissemination in SCLC patients not detectable on MRI before treatment, indicating that SRT treatment was useless in terms of CNS progression. Another explanation for the poor survival might be the overall poor prognosis due to the inborn aggressive behavior of recurrent SCLC.

The overall disease control rate (DCR) at a median time of three months was 84%, in line with previous studies [9, 23]. Notably, 30% of the treated lesions in our material were not available for evaluation, a situation that might affect the estimated DCR in this study. Several studies [16, 21, 26, 27] have reported tumor volume-related factors as significant predictors for local control. In the present study, we did not observe a significant impact regarding the PTV volume in the patient group receiving single-fraction SRT. However, the PTV volumes were mostly less than 8 cc, indicating a high likelihood of attaining local control.

Only four percent of patients in our study developed possible grade III–IV toxicity. Several previous studies reported similar results of a low incidence of severe toxicity (acute and/or late) due to SRT [15, 16, 18, 20], and the treatment was tolerable for most patients. The risk of toxicity due to cranial SRT increases with the increased radiation dose and size of the target volume [13, 14]. The volume of the brain receiving ≥ 12 Gy (V_{12}) has been shown to correlate with the increased risk of radiation necrosis, and the risk of toxicity to the brain increases drastically when V_{12} is > 5–10 cc [11]. However, we observed no correlation of increased acute toxicity with the size of PTV, large $V_{12,}$ or dose per fraction. Additionally, we observed no correlation between age and increased toxicity (Tab. 2). However, we showed that previously administered cranial RT is a significant prognostic factor for the increased risk of acute toxicity ($p = 0.03$), a finding that should be considered for SRT, side effect management and information for the patient.

The limitations of this study were mainly due to its retrospective nature, the clinical heterogeneity of the patient cohort and nonuniform treatment strategies. Additionally, the record keeping regarding toxicity was deficient, increasing the risk of data misinterpretation, and the assessment of local control may also be challenging in the postradiotherapeutic setting.

Conclusions

In conclusion, despite the shortcomings mentioned above, our study demonstrated that SRT due to brain metastases from primary lung cancer is a well-tolerated treatment. Patient selection for this treatment should not be affected by age or the extent of extracranial metastatic burden, performance status and extracranial disease progression should be considered, and smoke cessation is likely valuable even in this palliative setting. However, the goal of SRT for BMs is not only to improve survival but also to improve palliative treatment by inhibiting troublesome symptoms. In this context, predictive factors for survival may lose their value and studies on palliative cranial SRT should aim to assess patient-reported outcomes in addition to the response, toxicity and survival.

Conflicts of interest

The authors have declared no conflicts of interest.

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