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Mortality during or shortly after Curative-Intent Radio-(Chemo-)Therapy over the last decade at a large comprehensive cancer center

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ABSTRACT

Background and Introduction: Definitive surgical, oncological and radio-oncological treatment may result in significant morbidity and acute mortality. Mortality during or shortly after treatment in patients undergoing curative radio-(chemo)-therapy has not been studied systematically. We reviewed all curative radio-(chemo-)therapies at a large comprehensive cancer center over the last decade.

Materials and Methods: The institutional record was screened for patients who received curative-intent radio-(chemo-)therapy and deceased during or within 30 days after radiotherapy. Curative therapy was defined as prescribed dosage of EQD2 $\geq$ 50 Gy for radiotherapy alone and EQD2 $\geq$ 40 Gy for radiochemotherapies. Data on demographics, disease and treatment were assembled and assessed.

Results: Of 15,255 radiotherapy courses delivered at our center, 8,515 (56%) were performed with curative-intent. During or within 30 days after radio-(chemo-)therapy, 78 patients died (0.9% of all curative-intent courses). Median age of the deceased patients was 70 (IQR, 62–78) years, and 36% (28/78) were female. Median pre-therapeutic ECOG-PS was 1 (IQR, 0–2) and Charlson-Comorbidity-Index was 3+ (IQR, 2–3+). The most common primary malignancies were head and neck cancer (33/78; 42%) and central nervous system tumors (13/78; 17%). Peritherapeutic mortality varied by primary tumor, with the highest prevalence observed in head and neck and gastrointestinal cancer patients with 2.9% (33/1,144) and 2.4% (8/332), respectively. Among patients with known cause of death (34/78; 44%), tumor progression (12/34; 35%) and pulmonary complications/causes (11/34; 35%) were most common. On multivariable regression analysis, a worse ECOG-PS was associated with a relatively earlier *peri*-radiotherapeutic death ($p = 0.014$).

Conclusion: Mortality during or within 30 days of curative-intent radio-(chemo-)therapy was low, yet highest for head and neck (2.9%) and gastrointestinal tumor (2.4%) patients. Reasons for these findings include rapid tumor progression in some cancers, good patient selection, with ECOG-PS being most useful and predictive for avoiding early mortality. Future research should help refine predictors for *peri*-RT mortality.

Abbreviations: ASTRO, American Society of Radiation Oncology; BASEC, Business Administration System for Ethics Committees; CCI, Charlson-Deyo Comorbidity Index; CCCZ, Comprehensive Cancer Center Zurich; CI, Confidence interval; CCI, Charlson Comorbidity Index; ECOG-PS, Eastern Cooperative Oncology Group performance status; EQD2, Equivalent of 2Gy single dose; EMR, Electronical medical records; GPA, Graded Prognostic Assessment; HNC, Head & neck cancer; ID, Identifier; IMRT, Intensity-modulated radiotherapy; IQR, Interquartile range; MVA, Multivariable regression analysis; NCDB, National Cancer Data Base; NSCLC, Non-small cell lung cancer; RCT, Radiochemotherapy; RPA, Recursive Partioning Analysis; RT, Radiation therapy; SAE, Severe adverse event; TPS, Treatment planning system; USZ, University Hospital Zurich; UVA, Univariable regression analysis.

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Introduction and background

Modern oncological care offers cure or long-term overall survival for an ever-increasing share of patients. Yet definitive surgical, oncological and radio-oncological therapy regimens are not without toxicity, and may even result in significant morbidity and acute mortality. Mortality during or shortly after treatment, often termed *peri-radiotherapeutic (peri-RT) mortality*, in patients undergoing curative-intent radiotherapy (RT) or radiochemotherapy (RCT) have not been studied systematically. Only a few site-specific and one more broadly conceptualized report are published in the pertinent literature to date [1,2].

In the recent past, two abstracts, both presented at annual meetings of American Society of Radiation Oncology (ASTRO), pointed towards the lack of analysis and evidence in the field of *peri*-RT mortality despite a growing focus on quality assurance, patient safety and quality-of-life in the fields of radiation oncology and oncology. In 2016, *Dyer et al.* reported on 78 patients whose death was associated with RT at a single cancer center. The authors assessed the prevalence of *peri*-RT mortality, identified predictors for death during or shortly after RT, and put forth an analysis of what deaths might have been preventable [3]. Five years later, in 2021, *Xiang et al.* identified more than one million patients through the US-American National Cancer Database (NCDB) who deceased during or within 30 days after non-palliative RT. In this abstract, the authors also reviewed the prevalence of and predictors for *peri*-RT mortality [4]. Moreover, some studies exist which examine *peri*-therapeutic death in more narrowly defined sub-groups of oncological patients. For example, *Wallington et al.* (2016) looked at 30-day mortality after systemic anticancer treatment in patients with breast and non-small cell lung cancer (NSCLC) in England on a population basis [5]. And *Hamilton et al.* (2017) assessed early mortality after RT for patients with head and neck carcinoma (HNC) at a cancer center in Canada [1].

In order to contribute to this growing body of literature scrutinizing the prevalence of *peri*-RT mortality, we screened our institutional database for patients who received curative-intent RT or R(C)T and died during and within 30 days after therapy at our comprehensive cancer center over the last decade. The primary aim of this analysis is to establish the prevalence of *peri*-RT mortality as a proxy for the quality of care and patient safety at our Department of Radiation Oncology. The secondary aim of this study will be the identification of predictors for *peri*-RT mortality in this highly select group of patients at a single cancer center. By conducting this analysis, we not only closely examine practice at our institution, but also aim at encouraging other centers and departments to conduct similar analyses. Such single-institution studies might help pave the way for multi-center, national-level or disease-specific assessments, thereby further highlighting the importance of risk–benefit calculus prior to prescribing definitive, aggressive oncological treatments.

Materials and methods

Patient screening process

The institutional treatment database was screened for patients who had received curative-intent R(C)T between January 2011 and December 2021 at our center and deceased during or within 30 days after radiotherapy completion/end. This cut-off was chosen, as it was reported in the two quoted ASTRO abstracts [3,4], and also because it is commonly used in the palliative RT literature when assessing therapy close to end-of-life [6,7]. While it is an open question of whether 30-, 90- or even 180-day mortality after RCT should be regarded as quality measure, the contrast between a high potential for cure after a weeks-long therapy regimen versus death during or shortly after therapy seems most pronounced [2,8]. Curative therapy was defined as curative-intent per the treating radiation oncologist, with a prescribed dosage of an equivalent in 2 Gy single dose (EQD2) $\geq$ 50 Gy for RTs alone, EQD2 $\geq$ 40 Gy for RCTs and even lower dose cut-offs for lymphoma patients. Cases of local ablative treatments to oligometastatic disease were excluded.

Variables and data collection

Data on demographics, disease and treatment parameters were assembled. Treatment parameters were automatically extracted from the treatment planning system (TPS) ARIA®. This included patient and RT course identifier, primary tumor histology, date of birth, gender, date of death, treatment site, treatment intent, start date, end date, therapy completion status, fractionation, dosage, prescribed total dose, and administered total dose. Data on clinical variables was obtained from the electronical medical records (EMR) system KISIM®. Variables manually extracted from the EMR included date of primary diagnosis, initial tumor staging, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) at pre-RT consult, comorbidities as captured by the Charlson Comorbidity Index (CCI), history of prior RT or surgery, concurrent systemic therapy status, cause of death, place of death, hospitalization status, and autopsy status.

Data and statistical analysis

Upon extraction of the data from the TPS and EMR, it was streamlined in the spreadsheet program Microsoft® Excel® (V.16.0). Descriptive summary statistics were computed for all variables under study; to quantify the distribution of values, the mean and interquartile range (IQR) were used. Prevalence of *peri*-RT mortality was calculated by dividing the number of deceased patients in a certain time period over the number of all patients treated during that same time period. Peri-RT prevalence was calculated both for the entire study period and for every year individually, using both total number of patients treated and total number of patients treated curatively as the denominator. Univariate and multivariate regression analysis (UVA/MVA) were used to identify predictors for *peri*-RT mortality. Potential predictors were chosen based on clinical experience and expertise and prior publications [3,4]; given the 78 data points in our data set, we limited the number of independent variables to six for regression analysis. Age (years) and EQD2(Gy) were treated as continuous variables; CCI as categorical variable, with a point score of "0" as reference category; and systemic therapy status (yes vs. no), primary tumor (HNC vs. all other) and ECOG (>1 vs. ≤ 1) as binary variables, employing the median where applicable to categorize variables. The UVA and MVA models were both run with the same six explanatory variables, which were regressed on days to *peri*-RT death as a dependent variable (dichotomized by the median value of days between end of R(C)T and death). The cut-off for statistical significance was set at $p < 0.05$, as is common in medical research. Statistical analysis was carried out with the software package *R*® (Version R-4.2.2 for Windows).

Ethical approval

This study was approved by the Swiss Cantonal Ethics Committee before the initiation of the project (BASEC ID #2019-02488). All analysis and choice of methodology were carried out in accordance with relevant guidelines and regulations or the Declaration of Helsinki. Institutional general consent was obtained from subjects or their legal guardian at the time of therapy consent.

Results

Prevalence of peri-RT mortality

From January 2011 to December 2021, 15,255 RT courses were delivered at our center, 8,515 (55.8%) were prescribed with curative-intent. During or within 30 days after R(C)Ts, 78 patients had died, which represents 0.5% and 0.9% of all RT courses and of all curative-

intent RTs prescribed, respectively. The prevalence of the *peri*-RT mortality over the years was comparatively small and showed little variation, both when compared with all RTs or curative-intent R(C)Ts (see Fig. 1). Among the four largest patient subgroups, cancer-specific *peri*-RT mortality varied by primary tumor, ranging from 2.9% (n = 33/n = 1,144) and 2.4% (n = 8/n = 332) in head and neck cancer (HNC) and gastrointestinal tract (GIT) cancer patients, to 2.1% (n = 13/n = 629) and 1.8% (n = 12/n = 661) in central nervous system (CNS) and NSCLC patients.

Patient and treatment characteristics

The median age of the 78 patients under study was 70.3 (IQR, 62.3–78.3) years. A proportion of 35.9% (28/78) of patients were female. The most common primary malignancies were HNC (33/78; 42.3%), CNS tumors (13/78; 16.7%), and NSCLC; 12/78; 15.4%). No patient had distant metastasis at time of diagnosis. Charlson-Comorbidity-Index (CCI) was 3+ (IQR, 2–3 +) and median pre-therapeutic ECOG-PS was 1 (IQR, 0–2) among patients with documented comorbidity status (78/78; 100%) and performance (68/78; 87.2%), respectively. The site of RT was the primary tumor for 75 (96.2%) patients, and a metastatic site for 3 (3.8%) patients. Median prescribed dose was 65.6 Gy (interquartile range (IQR), 50.0–70.0 Gy), and median RT duration was 43 (IQR, 29–52) days. Thiry-two patients (41.0%) had been prescribed a concurrent chemotherapy. Almost one fifth of patients (15/78; 19.2%) had had surgery prior to R(C)T, and two patients (2.6%) had undergone a prior course of RT to the same anatomical site years before (re-irradiation type 1) [9]. The median number of days between treatment start and death was eight days (IQR, 2–20); two patients died before the first fraction was administered. An overview of basic patient and treatment characteristics is displayed in

Table 1
Summary of basic patient and treatment characteristics.

Variable	Data (N = 78)
Age in years, median (IQR)	70.3 (62.3–78.3)
Female gender, n (%)	28 (35.9)
Primary tumor, n (%)	
• Head & neck cancer	33 (42.3)
• Central nervous system	13 (16.7)
• Non-small cell lung cancer	12 (15.4)
• Gastrointestinal cancer	8 (10.3)
• Other[1]	12 (15.4)
No metastasis at time of diagnosis, n (%)	78 (100)
CCI, n (%)	
• 0	5 (6.4)
• 1	8 (10.3)
• 2	10 (12.8)
• 3	12 (15.4)
• 3+	43 (55.1)
Pre-RT ECOG-PS, median (IQR)	1 (0–2)
Site of RT, n (%)	
• Primary tumor	75 (96.2)
• Metastatic site	3 (3.8)
Prescribed dose, median (IQR)	65.6 (50.0–70.0)
RT duration in days, median (IQR)	43 (29–52)
Concurrent systemic therapy, n (%)	32 (41.0)
Surgery before RT, n (%)	15 (19.2)
Prior course of RT, n (%)	2 (2.6)
Time to death in days, median (IRQ)	8.0 (2.0–19.8)

Acbbreviations: CCI = Charlson morbidity index; ECOG = Eastern Cooperation Oncology Group performance status; EQD2 = Equivalent of 2 Gy single dose; Gy = Gray; IQR = Interquartile range; RT = Radiotherapy.

[1] Includes bone/soft tissue cancer (1), breast cancer (1), genitourinary cancer (1), lymphoma (2), prostate cancer (2), skin cancer (2), small-cell lung cancer (2), and other cancers (1).

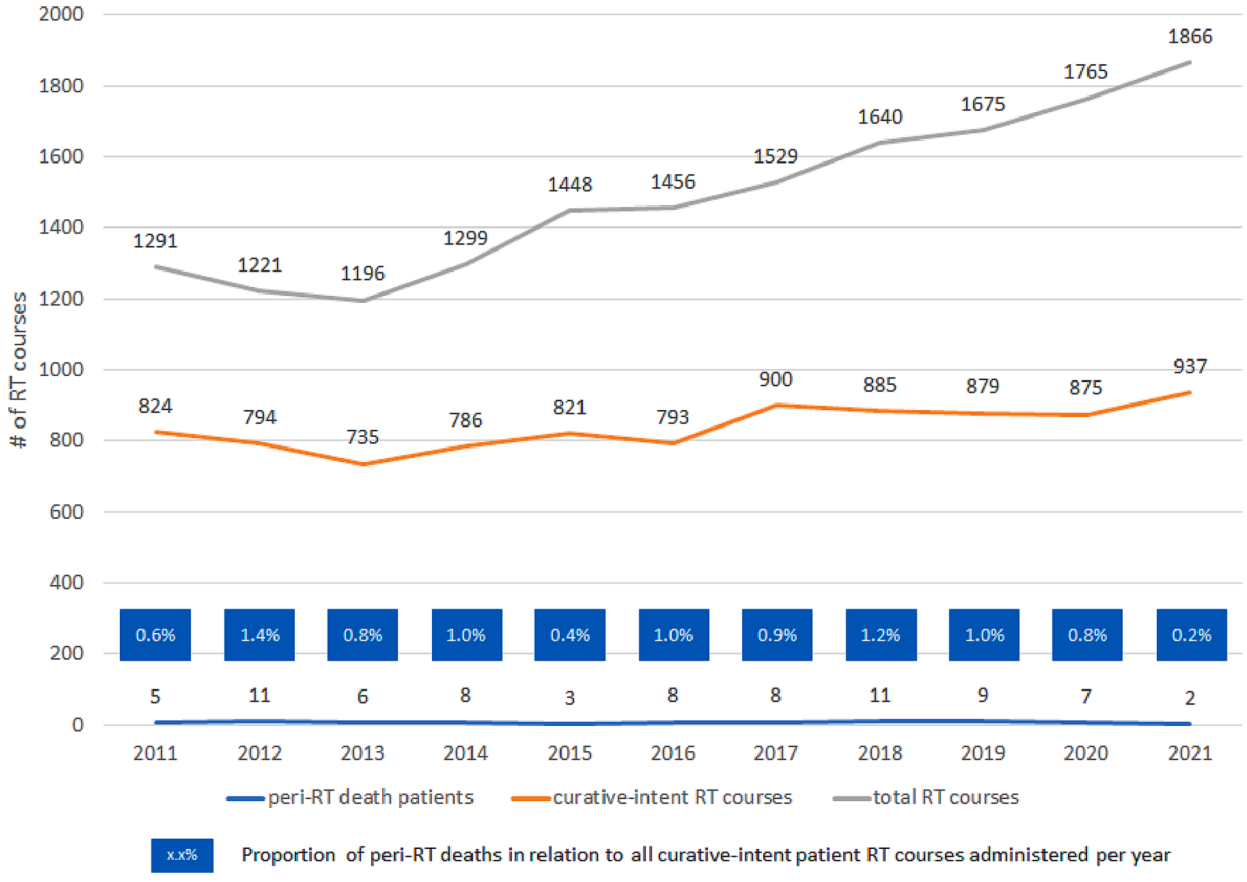

Fig. 1. Prevalence of *peri*-RT mortality at CCCZ over time. Abbreviations: CCCZ = Comprehensive Cancer Center Zurich, RT = Radiotherapy.

Table 1.

Causes of death

Cause of death was known/ reconstructable via retrospective EMR review for 34 (43.5%) patients, ten (29.4%) had an autopsy. The three most common causes of *peri*-RT death were tumor progression (12/34; 35.3%), pulmonary complications/causes (11/34; 32.4%) and cardiac complications/causes (6/34; 17.6%). Cause of death remained unknown for 17 (21.8%) patients (see Table 2).

Predictors for peri-RT mortality

On both UVA and MVA, a worse ECOG-PS (>1 vs. ≤ 1) was associated with an earlier *peri*-RT mortality (p-values: <0.05 and < 0.01, respectively). No association was detected for age, concurrent chemotherapy, primary tumor, EQD2(Gy), and CCI, neither on UVA and MVA (see Table 3).

Discussion

Dyer et al. (2016), who reported on 78 patients whose death occurred during the RT period at a single American cancer center between 2000 and 2016 reported a *peri*-RT mortality of 0.55%. However, the authors did not include patients who died within the month following RT completion, and they also limited reported deaths to those "associated with radiation treatment", which might have led to a downward bias of the mortality figure [3]. *Xiang et al. (2021)* reported an average prevalence of *peri*-RT mortality of 2.8% for approximately 1.32 million patients who received a non-palliative RT in the USA between 2004 and 2016, employing the definition of death during or within 30 days of RT completion/end. The authors also highlighted that *peri*-RT mortality hugely varied by primary tumor, ranging from 0.1% for breast cancer to 8.6% for CNS malignancies [4]. *Dixon et al. (2007)*, in assessing the treatment of 1,116 HNC (excl. laryngeal cancer) patients treated at The Christie HNS Foundation Trust between 2011 and 2015, reported a mortality of 4.7% during or within 90 days of therapy completion [10]. In a retrospective chart review, *Hamilton et al.* (2017) also assessed 90-day mortality after radical RT for HNC patients treated between 1998 and 2014 at a cancer center in Canada and found a prevalence of 3.6% [1]. *Katopodis et al.* (2004) reviewed 60-day mortality of 1,720 GIT cancer patients, treated in randomized controlled trials at the Royal Marsden Hospital in London, and found peritherapeutic mortality to range between 0.2% (adjuvant colorectal cancer) and 12.9% (pancreatic cancer) [11]. Disease-specific mortality in our sample of 78 deceased patients was lower (HNC: 2.9%; NSCLC: 1.8%; GIT: 2.4%). Also, the overall, disease-agnostic prevalence with 0.9% was at the lower end of the *peri*-RT mortality spectrum found in the literature. Various factors, which, taken together, can be taken to provide an indication for excellent oncological quality-of-care and a good patient selection, might have contributed to this finding: Modern radiotherapy technology, vigorous multidisciplinary tumor board discussions, and significant improvements in supportive patient management. This is also underscored by the fact that more than a third of patients with known cause of death died of rapid tumor progression rather than treatment-related toxicity.

Table 2
Causes of death during or shortly after curative radio(chemo-)therapy.

Variable	Data (n = 78)
Pulmonary complication/cause, n (%)	19 (31.1)
Tumor progression, n (%)	18 (29.5)
Cardiac complication/cause, n (%)	8 (13.1)
Multi-organ failure, n (%)	8 (13.1)
Neurological complication/cause, n (%)	4 (6.6)
Accident, n (%)	2 (3.3)
Gastrointestinal complication/cause, n (%)	2 (3.3)
Unknown cause of death, n (%)	17 (21.8)

Note: Ten patients had cause of death confirmed in an autopsy.

Table 3
Univariable and multivariable analysis for *peri*-RT mortality predictors.

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	1.03	1.00; 1.07	0.09	1.04	0.97; 1.12	0.3
Concurrent CTx	2.27	0.91; 5.92	0.08	2.82	0.68; 13.2	0.2
HNC vs. all other	1.18	0.48; 2.91	0.7	0.84	0.19; 3.57	0.2
EQD2 (Gy)	1.00	0.96; 1.04	0.8	1.00	0.93; 1.07	>0.9
CCI						
• 0	*(reference)*					
• 1	4.00	0.36; 98.9	0.3	0.64	0.02; 26.0	0.8
• 2	4.00	0.40; 94.4	0.3	0.94	0.03; 48.6	>0.9
• 3	2.00	0.20; 46.3	0.6	0.21	0.00; 12.4	0.4
• 3+	4.19	0.56; 85.6	0.2	0.21	0.00; 12.9	0.4
ECOG-PS > 1 vs. ECOG-PS ≤ 1	5.15	1.76; 16.7	**<0.01**	4.65	1.43; 17.1	**0.014**

Acbbreviations: CI = Confidence interval; CCI = Charlson comorbidity index; CTx = Chemotherapy; ECOG-PS = Eastern Cooperation Oncology Group performance status; EQD2 = Equivalent of 2 Gy single dose; Gy = Gray; HNC = Head & neck cancer; OR = Odds ratio.

While several variables such as ECOG-PS and CCI were not available in the TPS ARIA®, the group of deceased patients did indeed differ along some key dimensions when compared to national cancer epidemiology figures from Switzerland. For example, while the median age of patients who deceased during or shortly after R(C)T at our institution was 70 years, the median age at cancer diagnosis in Switzerland is 65 years [12]. With about 60% of patients who deceased during or shortly after R(C)T in our cohort being male, the share of male patients might have been overrepresented, while the tendency reflects the fact that cancer incidence and mortality are higher in men than women in Switzerland (five-year all-cancer incidence, male: 24,500, female: 20,500; five-year all-cancer mortality, male: 9,500, female: 7,800) [13]. Moreover, of the four most common cancers in Switzerland (prostate, breast, lung, colorectal), only NSCLC and GIT cancers ranked in the top 4 in the group of deceased patients in our cohort [13].

In our patient series, only ECOG-PS was found to be a predictor for earlier *peri*-RT mortality, while all other factors such as age, primary tumor site, concurrent chemotherapy, prescribed dose and comorbidities were not significantly with comparatively earlier *peri*-RT mortality. In the abstracts of *Dyer et al. (2016)* and *Xiang et al. (2021)*, who conducted predictor analyses using control groups, various factors were identified as predictive for periRT mortality. While neither abstract explicitly refers to performance status, *Dyer et al. (2016)* found that disease subsite is strongly correlated with increased mortality [3], and *Xiang et al. (2021)* showed that cancer stage, older age, baseline comorbidity, and lack of private insurance were major predictors for *peri*-RT mortality in the USA [4]. Concurrent use of chemotherapy and the use of intensity-modulated radiotherapy (IMRT) were found to be protective factors in different studies [4,10]. In a benchmarking exercise of different trusts with respect to 30-day mortality after systemic anticancer treatment in patients with breast and NSCLC cancer in England, *Dixon et al. (2007)* identified increased age and worse general well-being, defined as a performance status of 2–4, as predictors of *peri*-RT mortality [5]. Hence while our patient series confirms that a good performance status constitutes an important basis for definitive R(C)T, our regression analysis was underpowered to help detect the potentially

predictive value of at least some of the other covariates.

The science (or art) of fit-for-therapy, disease course or overall survival prediction has gained increased attention. Discussion points concern the identification of both the right end points as well as the clinically viable predictors. While *Dyer et al. (2016)* and *Xiang et al. (2021)* argued that periRT mortality until 30 days after treatment is a relevant endpoint [3,4], clinical trial protocols include requirements to report 90-day mortality [14,15], and other authors claim that neither end-point are relevant quality-of-care indicators [2]. There is also a huge variety in terms of predictor identification methodologies and proposed predictors, ranging from univariable, for example, performance status only [16], to multivariable prediction models [17], and cover both palliative [18–20] and curative domains [21]. In the metastatic setting, tools such as the recursive partioning analysis (RPA) [22] and graded prognostic assessment (GPA) [23] are employed for brain metastasis patients. In the primary setting, HNC and glioblastoma scores have been proposed, yet their routine clinical use and benefit remain unclear [24,25]. Across all primary cancers, ECOG-PS is the most regularly and reliably used therapy selection criterion in our center. Even in this small patient series, it was confirmed as a predictor for relatively earlier periRT mortality. Taken together with the fact that disease-specific periRT mortality for HNC, GIT cancer, CNS cancer, and NSCLC patients was comparatively low in our series, this underscores both the importance of routinely using and re-evaluating ECOG-PS during ongoing treatment as well as the good patient selection and oncological management practiced at our center.

It is a strength of this study to be the first to systematically scrutinize *peri*-RT mortality at a large comprehensive cancer center in Switzerland. Limitations of this study arise from its retrospective nature and small sample size. The retrospective character of the study does not permit generalizations to other centers or patient populations; and the small sample size limited the statistical power so as to detect potentially genuine differences in examined variables, thus compromising the ability of this study to identify more *peri*-RT mortality predictors. We strongly encourage other institutions to conduct similar analyses, so as to enable a multi-center or national-level analysis, which will not allow for the identification of general *peri*-RT predictors, but also illuminate further cancer-specific differences, which in return will improve future patient selection and treatment recommendation.

In conclusion, death during or within 30 days of therapy completion/end of curative-intent R(C)T was low and highest for HNC and GIT cancer patients. ECOG-PS was predictive of relatively earlier periRT mortality. This indicates that risks and benefits were carefully weighed by treating physicians. Future research should aim to identify more predictors for *peri*-RT mortality and to develop mitigation strategies to further improve quality of cancer care and patient safety.

CRediT authorship contribution statement

Nicolaus Andratschke: Conceptualization, Project administration, Review & Editing.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

STL received a research grant from Varian, honoraria from Varian, and her husband is employed at Varian. PB cited research grants to the institution from ViewRay Inc. (Mountain View, CA, USA). NA has received grants from ViewRay Inc. and BrainLab and personal fees from AstraZeneca, Debiopharm, ViewRay and BrainLab, and non-financial support from ViewRay, all outside of the submitted work.

The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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