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Thirty-Day Mortality Following Systemic Anticancer Therapy

Evaluating Risk Factors Without Selection Bias in a Real-World, Population-Based Cohort From 2009 to 2019

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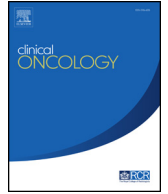
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Abstract

Aims: Risk factors for systemic anticancer therapies (SACTs) administered close to death derived from existing quality indicators are not directly applicable in the clinic, because they condition on future events, which leads to selection bias. This study aimed to adapt a previously suggested indicator for its use in a clinical context and to evaluate it in a real-world, population-based cohort of cancer patients.
Materials and methods: An improved version of the '30-day mortality after SACT' indicator suggested by Wallington *et al.* (*Lancet Oncol* 2016; 17:1203–16) was defined. All SACTs ($n = 16\ 622$) for all patients ($n = 10\ 213$) treated for common malignancies between 2009 and 2019 in the North Denmark Region were included. The results for the improved and Wallington's indicators were calculated and compared.
Results: Overall, the association between clinical variables and 30-day mortality following SACT was similar for both indicators, except for the 75+ years age group. However, Wallington's indicator showed varying absolute risk when comparing values for quarterly and yearly observation intervals. The improved and Wallington's indicators showed large differences between curative (1.0% and 1.1%, respectively) and palliative SACTs (9.1% and 11.7%, respectively). For palliative SACTs, different types of malignancy presented with large variations for the improved indicator, ranging from above 10% for gastroesophageal, pancreatic and lung cancers to below 4% for prostate cancers. The value of the improved indicator was significantly lower in the last years of the study period compared with the 2009–2011 period. The type of malignancy was also associated with significant differences.
Conclusions: We defined an indicator adapted to the clinical context evaluating 30-day mortality following SACT. This indicator can be used to identify risk factors to help with clinical decision-making. A significant downward trend was observed in the 30-day mortality following palliative SACT over an 11-year period.
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Key words: Antineoplastic drugs; monitoring tool; mortality risk factors; short-term mortality

Introduction

Systemic anticancer therapies (SACTs) often require lengthy drug administration procedures at hospitals and frequently induce severe side-effects [1–4]. Patients with limited residual life expectancy may not benefit from the treatment and only experience the short-term side-effects, thus reducing the patient's quality of life [5]. SACT should be avoided in these cases [6].

To monitor the usage of SACT near the end of life, primarily two approaches have been used. One, proposed by Earle *et al.* [7], considers exclusively patients who die from cancer. Although the criterion on the cause of death is not an issue for monitoring, it becomes a problem when calculating risk factors. Indeed, including only patients who died from cancer leads to a selection bias in the cohort definition by conditioning the inclusion on future events [8]. Conditioning on death from cancer will, for example, exclude long-term survivors who died from other causes.

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Another approach was proposed by Wallington *et al.* [9]. It suggests examining 30-day mortality from the start of the last SACT cycle in a calendar year. Their indicator, referred to as Wallington's indicator in the following, does not condition on death or its cause and, thus, allows for more prospective studies. As Wallington's indicator only considers the last SACT given within a chosen observation interval for each patient, there is a selection bias towards inclusion of later lines. This selection bias may thus lead to unreliable calculation of risk factors for use in a clinical context.

This study aimed to adapt the end point of Wallington's indicator to improve the clinical applicability. A second aim was to compare risk factors found with both indicators in the same dataset. The final aim was to obtain standard values for 30-day mortality following SACT for the improved indicator, over the period 2009–2019 for the most common solid cancers in the North Denmark Region.

Materials and Methods

The Improved Indicator

SACT is defined as treatment including antineoplastic agents (i.e. Anatomical Therapeutic Chemical [ATC] classification code L01) [10]. This excludes endocrine treatments (ATC code L02) and supportive drugs such as biphosphates (ATC code M05BA) or antiemetics and antinauseants (ATC code A04). A cycle is defined as a set of drug prescriptions given on consecutive days. A SACT regimen is defined as a treatment based on the drugs used and the administration protocol. Consecutive cycles with the same regimen were grouped as one SACT, if the interval between two consecutive cycles was less than 60 days. SACTs were characterised using the regimen names, e.g. FOLFOX, to obtain their intent, palliative or curative. The line number represents the number of palliative SACTs administered to the patient. Some regimens can be chosen with either curative or palliative intent and were referred to as multi-intent regimens.

For each SACT, a dichotomous outcome was considered, describing whether the patient died within 30 days of the start of the last cycle of this SACT. Thus, the value for the improved indicator in a given observation interval was the average of the 30-day mortality outcomes for all SACTs that ended in this interval (see Figure 1). By contrast, only the last SACT that ended in the interval for each patient was used to calculate Wallington's indicator. For example, if a patient received two SACTs in an observation interval, only the outcome of the second SACT was considered.

Study Design and Participants

All patients from the North Denmark Region diagnosed with solid tumours before 31 December 2019 and alive after 1 January 2009 ($n = 29\,937$) were screened using the Patient Administrative System (PAS) from the North Denmark Region based on the diagnosis codes. Among these patients, 24 496 had one of the included malignancies (see Supplementary Table S1). In the period 2009–2019, 10 672 patients completed a SACT without being referred to other regions. Among these patients, 459 were excluded due to their participation in clinical trials. The final cohort of 10 213 patients received 16 622 SACTs (see Supplementary Figure S1).

The clinical data were extracted from the PAS and the treatment data were obtained from the prescription software ARIA OIS for Medical Oncology v13.7 (Varian Medical Systems, Palo Alto, CA, USA) (MedOnc). The PAS data consisted of all diagnoses and procedures coded according to the Danish Disease Classification System [11]. This classification system is similar to the ICD-10 classification for diagnoses. Dates of death were obtained from the Danish Civil Registration System (CPR). Data for each SACT consisted of gender, age, comorbidities according to Charlson's Comorbidity Index [12], current malignancy, treatment intent (curative or palliative), regimen, year at the start of treatment, line number and death within 30 days of the start of the last cycle. The comorbidities were extracted from the diagnosis codes found in the PAS (see Supplementary Table S2) and updated at each SACT. Only non-cancer-related comorbidities seen in at least 1% of the patients were considered as cancer type and treatment intent were considered independently. This included myocardial infarction, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus and chronic kidney disease.

Ethical Approval and Registration

According to Danish legislation, registry projects do not require patient consent and ethical approval, they must only be registered at the data responsible host institution. This study was part of a project registered at the Research Project Inventory of the North Denmark Region (reg. number 2019–41).

Statistical Methods

The improved and Wallington's indicators were both calculated over the 11-year period per diagnosis and treatment intent as well as for all diagnoses per year and treatment intent. Wallington's indicator was calculated with an observation interval of 1 year, taking into consideration only the last cycle of the last SACT for each patient who ended a SACT in each interval. An observation interval was defined as an individual time block for which a value of the indicator was calculated. The study period was therefore decomposed into multiple disjoint observation intervals each with an associated value for the indicator. To estimate the effect of the observation interval, Wallington's indicator was also calculated with an observation interval of a quarter, leading to 44 values,
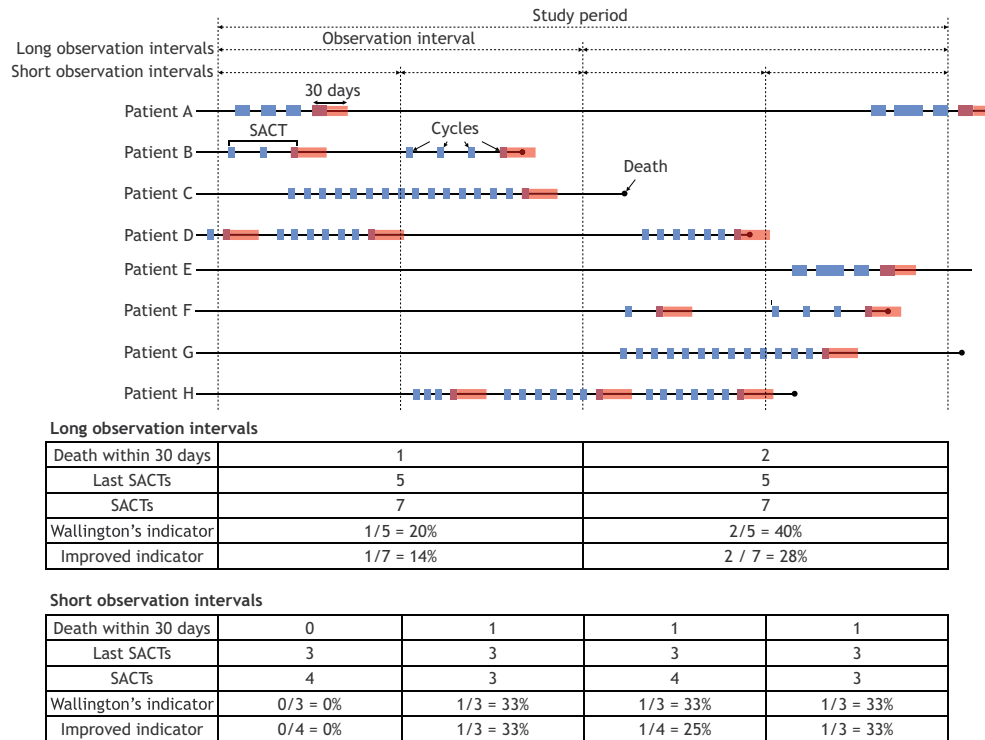
Long observation intervals

Death within 30 days	1	2
Last SACTs	5	5
SACTs	7	7
Wallington's indicator	1/5 = 20%	2/5 = 40%
Improved indicator	1/7 = 14%	2 / 7 = 28%

Short observation intervals

Death within 30 days	0	1	1	1
Last SACTs	3	3	3	3
SACTs	4	3	4	3
Wallington's indicator	0/3 = 0%	1/3 = 33%	1/3 = 33%	1/3 = 33%
Improved indicator	0/4 = 0%	1/3 = 33%	1/4 = 25%	1/3 = 33%

Fig 1. An example of a calculation of the improved indicator compared with Wallington's indicator using two different lengths for the observation interval on the same study period for eight patients receiving 14 systemic anticancer therapies (SACTs). The impact of the duration of the observation interval is illustrated in both cases using two interval lengths, the long observation interval length being twice the short observation interval one. In this example, the study period is either split into two long observation intervals or four short observation intervals. The limits of the observation intervals are represented with vertical dashed lines. The outcome of a SACT is considered for the calculation of the values of the indicators for an observation interval if the SACT ends in this interval. The last SACTs value represents the number of SACTs ended in an observation interval when considering only the last SACT, or, in other words, it is the number of patients who ended a SACT in the considered observation interval. The difference between the values for the last SACTs and the SACTs illustrates the exclusion of some SACTs and therefore the selection bias.

as opposed to the corresponding 11 yearly values. Additionally, the improved indicator for palliative treatments was calculated over the 11-year period per line number and per drug combination.

A multivariate logistic regression was carried out for both indicators using period, age, gender, comorbidities, number of treatment lines and type of malignancy as independent variables to identify potential risk factors. Death within 30 days of the start of the last cycle of either each SACT or the last SACT in a given observation interval was used as the dependent variable for the improved and Wallington's indicators, respectively. The corresponding effect estimates are presented as odds ratios. A threshold of 0.05 was used to define the statistical significance of *P*-values and 95% confidence intervals were used for the odds ratios and survival estimates.

Thirty-day mortality per diagnosis, line number and regimen were also calculated, for which only SACTs given in first or second line were considered.

Data management and statistical analyses were carried out using SAS Enterprise Guide 8.3 (SAS Institute, Cary, NC, USA) and Python 3.8 in Jupyter notebooks [13]. The Python library statsmodel v0.11 [14] was used for the regressions.

Results

Study Population

The characteristics of the study population are presented in Table 1. Most of the 10 213 patients included in this study were women (60%) due to the size of the female cancer cohorts (breast, ovarian and uterine cancers, $n = 3331$).

Patients treated for advanced or metastatic disease received an average of 1.7 SACT lines. On average, prostate cancer patients received only 1.3 lines, whereas breast cancer patients were treated on average with 2.3 lines. For lung, pancreatic and prostate cancer, patients were predominantly given palliative SACTs (87%, 88% and 98%, respectively). In contrast, breast cancer patients mainly received curative SACTs (59%).

The Improved Indicator Compared with Wallington's Indicator

Per Diagnosis and Intent

As seen in Table 1, the 30-day mortality following SACT was higher for palliative SACTs than for curative SACTs

across malignancies (9.1% versus 1.0% for the improved indicator, 11.7% versus 1.1% for Wallington's indicator).

Considering all intents, there were large disparities between malignancies, ranging from below 4% for breast and uterine cancer SACTs (2.4% and 3.0% for the improved indicator, respectively, and 2.9% and 3.5% for Wallington's indicator, respectively) to above 11% in 30-day mortality for lung and pancreatic cancer SACTs (11.4% and 12.1% for the improved indicator, respectively, and 14% and 14.5% for Wallington's indicator, respectively).

For palliative SACTs, the 30-day mortality was above 10% for lung, gastroesophageal and pancreatic cancers (12.9%, 10.6% and 13.8% for the improved indicator, respectively, and 16.3%, 13.4% and 16.7% for Wallington's indicator, respectively), whereas it was less than 4% for prostate cancer (3.5% for the improved indicator, 3.8% for Wallington's indicator). For curative SACTs, the 30-day mortality was less than 2%, except for brain, ovarian and prostate cancers (3.2%, 5.4% and 7.7% for the improved indicator, respectively, and 5.0%, 8.8% and 9.1% for Wallington's indicator, respectively).

Overall, the 30-day mortality with Wallington's indicator was consistently higher than with the improved indicator, especially for curative SACTs given to ovarian cancer patients (8.8% versus 5.4%).

Per Year and Treatment Intent

Over time, the improved indicator showed an overall downward trend for the 30-day mortality from 6.9% in 2009 to 3.8% in 2019 (see Figure 2A). This decline was notable for palliative SACTs, decreasing from 11.8% in 2009 to 5.8% in 2019, whereas the 30-day mortality following curative SACTs remained low over the study period. A similar pattern was seen for Wallington's indicator with a downward trend, especially for palliative SACTs, which ranged from 13.9% in 2009 to 7.7% in 2019.

The mean difference between the quarterly and yearly 30-day mortalities for palliative SACTs was below 0.1% and above 2% for the improved and Wallington's indicators, respectively (see Figure 2B), illustrating the lack of comparability between values for Wallington's indicator calculated by different observation intervals.

Logistic Regressions

Figure 3 shows the results of multivariate regressions for both the improved and Wallington's indicators. No significant effect on 30-day mortality was found for comorbidities, gender, age group or line number in neither of the considered indicators. The period 2018—2019 was associated with a significant decrease in the 30-day mortality for both indicators compared with the period 2009—2011. A significant decrease was also found for the period 2015—2017 for the improved indicator. Lung, gastroesophageal and pancreatic cancer diagnoses had a significantly worse 30-day mortality than breast cancer using the improved indicator. Inversely, prostate cancer had a significantly better 30-day mortality compared with breast cancer.

Overall, no major difference could be found in terms of risk factors between the improved and Wallington's indicators. A difference was nevertheless observed for the 75+ years age group, with a significantly lower 30-day mortality for Wallington's indicator (odds ratio 0.82, confidence interval 0.69—0.99, $P = 0.040$), whereas it was far from significant for the improved 30-day mortality indicator (odds ratio 0.91, confidence interval 0.76—1.09, $P = 0.299$).

Thirty-day Mortality following Palliative Systemic Anticancer Therapies per Line Number and Drug Combination

The 30-day mortality using the improved indicator, shown for specific line number in Figure 4A, did not reveal any clear shared pattern across malignancies. For example, for gastroesophageal, colorectal and uterine cancers, the 30-day mortality was lower in the first line than in the second line. Conversely, for brain, pancreatic, prostate and urinary cancers, the 30-day mortality was lower in the second line than in the first line. For breast, lung and ovarian cancers, the 30-day mortality remained mostly stable between the first and second lines.

Large differences in 30-day mortality were observed for the four most frequently administered regimens by diagnosis group and line number (Figure 4B). Patients who received gemcitabine monotherapy tended to have high 30-day mortality (25.0% in the first line and 23.1% in the second line for pancreatic cancers and 24.1% in the first line for urinary cancers).

Discussion

Main Findings

We defined a quality indicator describing the 30-day mortality following the last cycle of SACT based on Wallington et al.'s [9] approach. This indicator is adapted to the clinical context by avoiding selection bias and summarises how often a SACT was followed by death within 30 days. Our proposed indicator allows for a more valid assessment of risk factors of the patients in a clinical context. However, limited differences were found between risk factors identified using the improved and Wallington's indicators for the present dataset. The exception was the 75+ year age group, which was identified as a significant risk factor using Wallington's indicator, whereas this was not the case with the improved indicator.

Overall, we report a significant downward trend for the 30-day mortality following SACT using both indicators for palliative SACTs over an 11-year period. This decrease was not necessarily expected, despite the increased worldwide attention to close-to-death treatment of cancer patients. Recent advances in cancer treatment could have led to an increase in 30-day mortality. For example, in the case of protein kinase inhibitors, some patients benefit from

Table 1

Study population characteristics (overall and based on the cancer diagnosis) and the improved and Wallington's indicators per diagnosis and systemic anticancer therapy (SACT) intent

	Overall	Brain	Lung	Breast	Gastro-oesophageal	Pancreatic	Colorectal	Ovarian	Uterine	Prostate	Urinary
N	10213	403	2563	2556	532	565	2081	507	268	450	288
Males (%)	40	60	50	1	75	55	57	0	0	100	69
Mean age at diagnosis years (range)	64 (19−94)	60 (20−84)	68 (33−93)	57 (25−89)	65 (32−84)	67 (39−87)	66 (19−94)	67 (19−88)	64 (21−89)	71 (48−87)	68 (37−89)
Tx	16622	907	4030	3979	922	809	3506	1108	395	580	386
Palliative Tx n (%)	10006 (62)	403 (44)	3505 (87)	1614 (41)	490 (53)	712 (88)	1855 (54)	464 (57)	117 (57)	567 (98)	279 (72)
Lines n (range)	1.7 (1−10)	1.7 (1−6)	1.6 (1−7)	2.3 (1−10)	1.5 (1−8)	1.4 (1−4)	2.0 (1−10)	1.9 (1−7)	1.4 (1−4)	1.3 (1−5)	1.4 (1−6)
30-day mortality − improved indicator											
For curative Tx % (ratio)	1.0 (59/6074)	3.2 (16/503)	1.1 (6/525)	0.2 (4/2353)	0.5 (2/430)	0.0 (0/97)	0.6 (10/1602)	5.4 (19/355)	0.0 (0/90)	7.7 (1/13)	0.9 (1/106)
For palliative Tx % (ratio)	9.1 (914/10,006)	7.7 (31/403)	12.9 (452/3505)	5.7 (92/1614)	10.6 (52/490)	13.8 (98/712)	5.8 (108/1855)	5.8 (27/464)	7.7 (9/117)	3.5 (20/567)	9.0 (25/279)
For multi-intent Tx % (ratio)	2.0% (11/542)	0.0% (0/1)	None	0.0% (0/12)	0.0% (0/2)	None	2.0% (1/49)	2.4% (7/289)	1.6% (3/188)	None	0.0% (0/1)
Overall % (ratio)	5.9 (984/16622)	5.2 (47/907)	11.4 (458/4030)	2.4 (96/3979)	5.9 (54/922)	12.1 (98/809)	3.4 (119/3506)	4.8 (53/1108)	3.0 (12/395)	3.6 (21/580)	6.7 (26/386)
30-day mortality − Wallington's indicator											
For curative Tx % (ratio)	1.1 (58/5125)	5.0 (15/299)	1.3 (6/484)	0.2 (4/2148)	0.7 (2/297)	0.0 (0/86)	0.7 (10/1409)	8.8 (19/217)	0.0 (0/73)	9.1 (1/11)	1.0 (1/101)
For palliative Tx % (ratio)	11.7 (907/7738)	10.1 (31/307)	16.3 (449/2762)	8.0 (92/1145)	13.4 (51/381)	16.7 (98/588)	7.8 (107/1364)	7.6 (25/327)	8.7 (9/103)	3.8 (20/524)	10.5 (25/237)
For multi-intent Tx % (ratio)	2.5% (11/447)	0.0% (0/1)	None	0.0% (0/12)	0.0% (0/2)	None	3.6% (1/28)	3.0% (7/236)	1.8% (3/166)	None	0.0% (0/1)
Overall % (ratio)	7.3 (976/13310)	7.6 (46/607)	14.0 (455/3246)	2.9 (96/3305)	7.8 (53/680)	14.5 (98/674)	4.2 (118/2801)	6.5 (51/781)	3.5 (12/342)	3.9 (21/535)	7.7 (26/339)

Age, average age at diagnosis in years; Lines, the number of palliative SACTs given to patients treated with at least one palliative SACT; Males, percentage of male patients; n, number of patients; Palliative Tx, number of SACTs given with palliative intent; Tx, total number of SACTs given.

Values between parentheses show the range for the 'Age' and 'Lines' columns, and the proportion in the percentage of palliative SACTs given among treatments with known intent for the 'Palliative Tx' column. The values shown for the improved and Wallington's indicators are in percentages. The 'Multi-intent' column contains the values for SACT regimens that can be used for both curative and palliative intents. The values between parentheses show the corresponding ratio. For the improved indicator, the numerator is the number of SACTs followed by the death of the patient within 30 days of the start of the last cycle, and the denominator is the total number of SACTs over the 11-year period. For Wallington's indicator, the denominator is the total number of patients who ended a treatment in a year, and the numerator is the number of these patients who died within 30 days of the start of their last cycle in the same year.
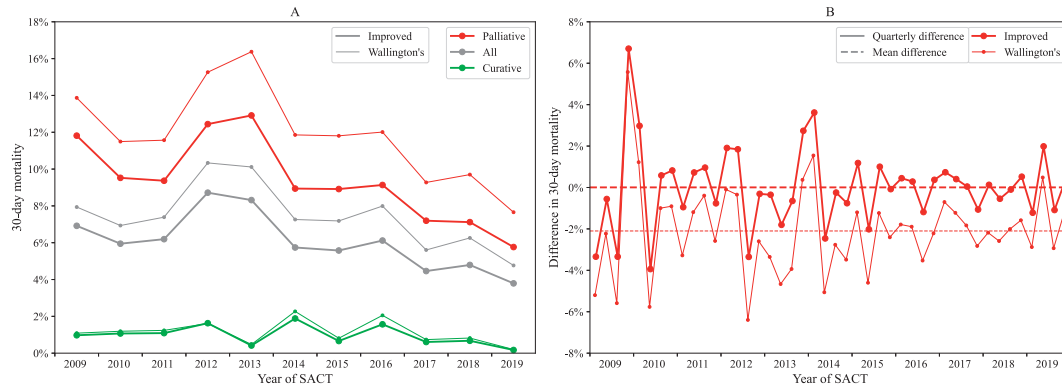
Fig 2. Thirty-day mortality per systemic anticancer therapy (SACT) intent and year (A) and the difference in 30-day mortality between the quarterly values and corresponding yearly values for palliative SACTs (B). The mean difference shows the mean of all differences between the quarterly and corresponding yearly values.

continued treatment close to death [15,16]. These treatments are nevertheless given in long cycles, typically of 6 weeks, which would mitigate this effect as we are considering the start of the last cycle. The fact that the 30-day mortality decreased over the period could be due to

an increased attention of the clinicians towards earlier discontinuation of treatment.

Our study also found large differences in 30-day mortality between malignancies and between treatment intent. Unsurprisingly, treatments administered to patients with

Variable	Patient-years	Pal. SACTs	Odds Ratio (OR)	Wallington's	P-value	Improved	P-value
Sex							
Female	4 177	5 435		Used as reference		Used as reference	
Male	3 673	4 571		1.16 (0.99, 1.36)	0.074	1.14 (0.98, 1.34)	0.095
Year							
2009-2011	1 829	2 219		Used as reference		Used as reference	
2012-2014	2 051	2 585		1.18 (0.98, 1.43)	0.089	1.09 (0.90, 1.31)	0.365
2015-2017	2 252	2 908		0.89 (0.73, 1.09)	0.261	0.80 (0.65, 0.97)	**0.023**
2018-2019	1 707	2 283		0.67 (0.53, 0.84)	**<0.001**	0.58 (0.46, 0.72)	**<0.001**
Age							
18-44	255	348		0.78 (0.48, 1.26)	0.308	0.79 (0.49, 1.26)	0.321
45-59	1 397	1 901		0.98 (0.81, 1.18)	0.807	0.93 (0.77, 1.12)	0.431
60-74	4 422	5 645		Used as reference		Used as reference	
75+	1 776	2 112		0.82 (0.69, 0.99)	**0.040**	0.91 (0.76, 1.09)	0.299
Comorbidities							
Myocardial infarction	285	348		0.95 (0.66, 1.38)	0.803	1.01 (0.70, 1.44)	0.978
Peripheral vascular disease	389	476		1.10 (0.81, 1.48)	0.541	1.14 (0.85, 1.53)	0.376
CVA or TIA	544	685		0.94 (0.71, 1.25)	0.673	0.96 (0.73, 1.26)	0.751
COPD	618	735		1.08 (0.85, 1.39)	0.516	1.16 (0.92, 1.48)	0.215
Connective tissue disease	209	262		1.07 (0.71, 1.61)	0.756	1.04 (0.69, 1.56)	0.853
Peptic ulcer disease	310	376		0.90 (0.62, 1.30)	0.570	0.90 (0.63, 1.29)	0.576
Diabetes	235	293		1.17 (0.80, 1.71)	0.425	1.20 (0.82, 1.74)	0.352
CKD	122	145		1.24 (0.73, 2.10)	0.430	1.30 (0.77, 2.18)	0.331
Line number							
1st line	4 793	6 041		Used as reference		Used as reference	
2nd line	1 791	2 334		1.08 (0.91, 1.28)	0.376	1.06 (0.90, 1.25)	0.492
3+ line	1 266	1 631		0.95 (0.77, 1.18)	0.664	1.01 (0.82, 1.25)	0.913
Diagnosis group							
Breast	1 158	1 614		Used as reference		Used as reference	
Brain	310	403		1.24 (0.79, 1.94)	0.347	1.41 (0.90, 2.19)	0.133
Lung	2 758	3 505		2.04 (1.58, 2.64)	**<0.001**	2.21 (1.72, 2.84)	**<0.001**
Gastroesophageal	387	490		1.59 (1.08, 2.34)	**0.019**	1.81 (1.24, 2.64)	**0.002**
Pancreatic	590	712		2.12 (1.53, 2.93)	**<0.001**	2.50 (1.81, 3.45)	**<0.001**
Colorectal	1 431	1 855		0.83 (0.61, 1.13)	0.233	0.90 (0.66, 1.22)	0.506
Ovarian	354	464		0.95 (0.60, 1.50)	0.840	1.07 (0.69, 1.68)	0.752
Uterine	103	117		1.07 (0.52, 2.20)	0.847	1.35 (0.66, 2.76)	0.410
Prostate	524	567		0.41 (0.24, 0.70)	**0.001**	0.55 (0.33, 0.93)	**0.026**
Urinary	235	279		1.26 (0.78, 2.05)	0.347	1.50 (0.93, 2.43)	0.097

Fig 3. Logistic regression results for palliative systemic anticancer therapies (SACTs) for the improved and Wallington's indicators. Year, year range at the start of the SACT; Age, age range of the patient at the start of the SACT. The comorbidities were defined as in Charlson's Comorbidity Index and the Patient Administration System codes used for each comorbidity are available in Supplementary Table S2. Only comorbidities with a prevalence of >1% in the cohort were considered. Note that using the line number with Wallington's indicator is theoretically not appropriate but was included for comparison with the improved indicator.
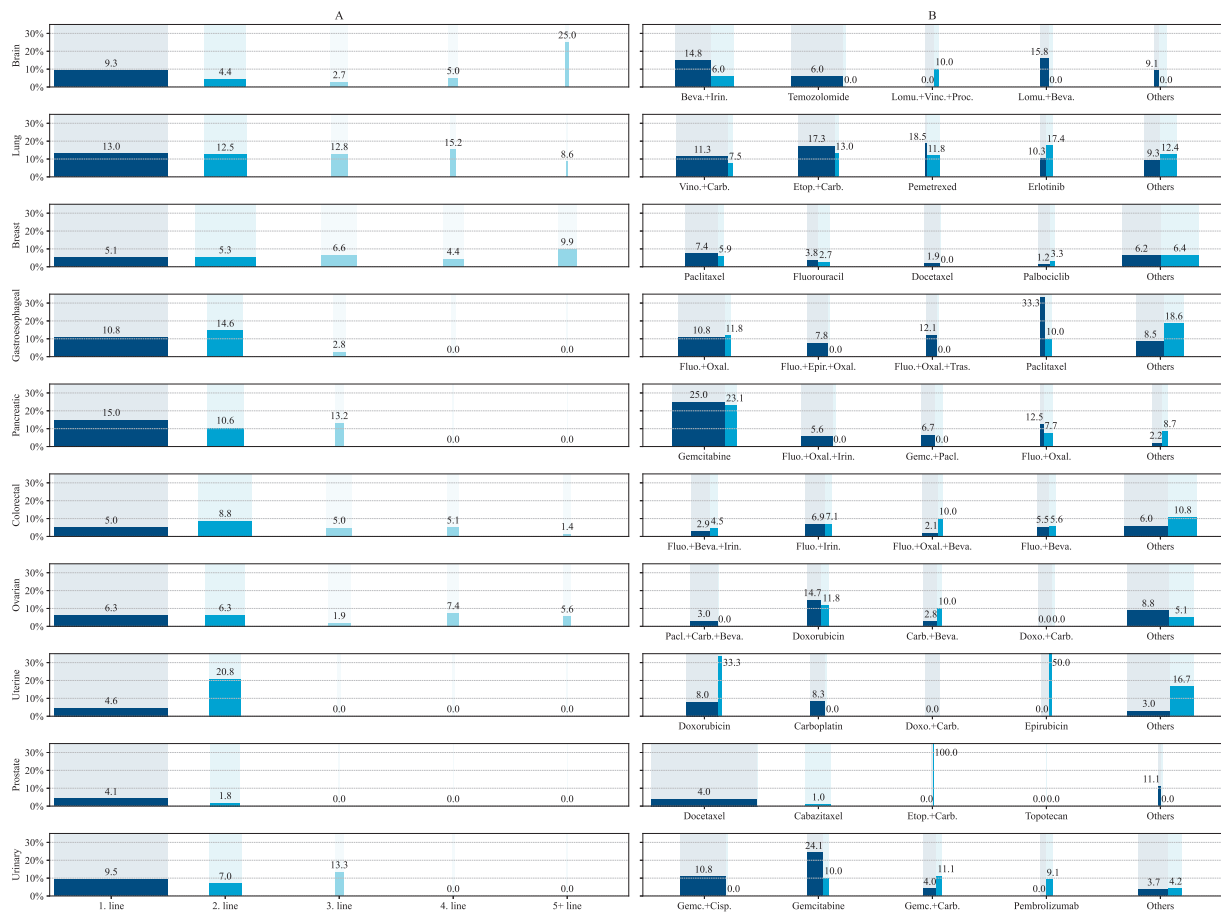
Fig 4. Thirty-day mortality following palliative systemic anticancer therapies (SACTs) per malignancy stratified by line number (A) and regimen (B). For each malignancy type, the width of the bar was proportional to the number of corresponding SACTs, normalised by the number of patients. For line number (A), the treatments after the fourth line were grouped in a '5+ line' category. For regimen (B), only the two first lines are included, and the corresponding top four regimens are displayed individually alongside other regimens grouped in the 'Others' category. Capecitabine is considered equivalent to fluorouracil and has thus been grouped with it. The same was true for panitumumab with cetuximab. Abbreviations: Beva., bevacizumab; Carb., carboplatin; Cisp., cisplatin; Doxo., doxorobucin; Epir., epirubicin; Etop., etoposide; Fluo., fluorouracil/capecitabine; Gemc., gemcitabine; Irin., irinotecan; Lomu., lomustin; Oxal., oxaliplatin; Pacl., paclitaxel; Proc., procarbazine; Tras., trastuzumab; Vinc., vincristine; Vino., vinorelbin. See Supplementary Tables S3 and S4 for the raw values.

metastatic or advanced cancer had the highest 30-day mortality compared with treatments given as curative SACTs. The 30-day mortality following curative SACTs was 2% for some years, which we consider unacceptably high, but the values in recent years have been consistently low.

The groups with the highest 30-day mortality were those including patients with metastatic lung, gastroesophageal and pancreatic cancers, all showing values above 10%. These values might partly be explained by widely spread tumour, several tumour-related symptoms and poor performance status, notably among lung cancer patients [17].

Overall, the number of treatment lines did not seem to have a clear impact on 30-day mortality, with different patterns observed across malignancies. The 30-day mortality was expected to be higher in the second line than in the first line due to the progression of the disease. However, for brain, pancreatic, prostate and urinary cancers, this was not the case. One explanation could be differences in toxicity profiles according to the type of malignancy and the line number. Another explanation could be that rapidly progressing disease may hinder the opportunity for second-line treatment, and only patients with less aggressively growing tumours are offered subsequent treatments.

Among the regimens, gemcitabine monotherapy had a high 30-day mortality. Gemcitabine is predominantly administered to frail patients with advanced urinary and pancreatic cancers [18], frailty that might not be taken well enough into consideration by clinicians, notably because this treatment might be the one and only option for these patients.

The considered comorbidities had no significant impact on 30-day mortality. This could be explained by their limited role in the 30-day mortality or by appropriate co-morbidity adjustment in the clinical treatment decision making.

Critical Assessment

The main strengths of this study are the population-based design, coverage of all the major cancer groups and

extension over a wide timeframe with a high level of detail from a single-centre setting. The single-centre setting could also be considered as a limitation. However, due to the homogeneity of the healthcare system and treatment guidelines in Denmark, we expect that the conclusions can be extrapolated to the entire Danish cancer patient cohort. Nevertheless, a national study is required to confirm this assumption. Additionally, pooling regimens of different types, for example cytotoxic and targeted, as well as cancer types with significantly different prognoses, such as small cell and non-small cell lung cancers, may lead to results that are not representative of any of the regimens or subtypes. Investigating the 30-day mortality for individual regimen types, cancer subtypes or rare malignancies (e.g. head and neck cancers and sarcomas) would require access to a larger cohort. This could be achieved by extending the study to the entire Danish cancer patient cohort, as done with another indicator by Mattsson *et al.* [19].

In this study, the main data sources were electronic health records and administrative data, which we refer to as healthcare data registries (HDRs). As such datasets are susceptible to biases, such as informed presence bias [20,21], we only considered actively followed patients, whose data are less prone to these biases.

One of the main advantages of using HDRs over quality databases is that they do not require additional reporting from clinicians. This makes it possible to build continuous quality monitoring tools. A disadvantage is the relative inaccessibility of some clinical parameters. For example, performance status, which is a known predictor of survival, is currently only recorded as text in patient journals.

Nevertheless, an increasing amount of healthcare data is currently being digitalised, and the quality of the stored data has been reported to be good, particularly in Denmark [22]. This should facilitate the development of HDR-based and clinically applicable quality indicators. An international consensus on the definition of a SACT is warranted as differences in the definition can significantly affect the results and impede the comparison of studies. We therefore use the WHO ATC classification as reference. We only included antineoplastic agents as defined by this classification, that is, drugs with an ATC code starting with L01. The endocrine therapies (ATC code starting with L02) were primarily excluded due to:

 (i) Their less severe toxicity profile;
 (ii) Oral administration, which implies fewer visits to the hospital, impeding the assessment of treatment compliance and impair the reporting in HDRs.

Furthermore, although these treatments are often included in studies following Earle *et al.*'s [7] approach, they were also excluded in Wallington *et al.*'s [9] study.

Benefits of the Improved Indicator

The '30-day mortality' end point is a common end point in healthcare systems, notably in surgery. This end point was used by Wallington *et al.* [9] and we thus decided to use this approach as a reference to define 30-day mortality. The main strength of our improved 30-day mortality indicator is that it can be used to evaluate risk factors for 30-day mortality following any SACT and can thus be used prospectively, i.e. to potentially adapt the quality of the treatment in the clinic. In contrast, risk factors calculated following Wallington *et al.*'s [9] approach can only be used adequately for the last SACT, which is only known in hindsight. This can lead to conflicting conclusions in the identification of risk factors using Wallington's indicator, as illustrated by the difference in significance for the 75+ year age group in our study.

By considering every SACT, this indicator also allows us to investigate the effect of the line number and the type of treatment used on the risk of treating too close to death without conditioning on future events and thus avoids selection bias. It is nevertheless important to note that the risk factors are only usable once the SACT is started and thus cannot be used to decide to start a SACT or not. Instead, it is intended to help clinicians better assess the risk of early mortality to stop an already started treatment in time.

An additional benefit of the improved 30-day mortality indicator is that it, in contrast to Wallington's indicator, remains unbiased across different choices of observation interval; for example, the 30-day mortality calculated for a quarter or a month can be directly compared with the 30-day mortality calculated over a year or a decade (see Figure 2B).

Comparison with Other Studies

Older studies have reported an increase [23,24] in late chemotherapy administration in cancer patients. However, in line with recent studies [25,26], we report a decrease in 30-day mortality over time, notably for palliative SACTs.

Compared with Wallington *et al.*'s [9] original results, we found similar results for breast cancer, with values of 0.2% compared with 0.3% for curative SACTs and 9.4% compared with 7.5% for palliative SACTs. For lung cancer, we found larger differences, with values for 30-day mortality for Wallington's indicator of 1.3% compared with 2.9% in Wallington *et al.*'s [9] study for curative SACTs and 17.8% compared with 10.0% for palliative SACTs. This can be partially explained by the difference in the inclusion criteria. This could also be due to recent developments in the treatment of lung cancer patients, notably the introduction of protein kinase inhibitor treatments.

Concerning other studies, the differences in inclusion criteria and end point definition limit the comparability with our study. This could explain the large variability in the results reported [23,26] and illustrate the need for more standardised definitions, as proposed here.

Perspectives

The improved indicator can be used to properly identify risk factors for high 30-day mortalities, with the objective of potentially improving the quality of life near the end of life and better utilising the available resources in the healthcare

system. This indicator for 30-day mortality following SACT should ideally be more focused on specific cancer diagnoses and treatment regimens in order to define recommendations and potential prognostic models to support the work of clinicians in daily clinical practice. More complex models allowing dynamic prediction and leveraging more extensive clinical data should also be built to help clinicians to decide when to stop an ongoing treatment.

Conclusions

We defined an improved quality indicator based on the approach followed by Wallington *et al.* [9] to evaluate the 30-day mortality following SACT. This indicator can be used to identify clinical risk factors for increased 30-day mortality and stays consistent across different choices of observation intervals. Using this indicator, we noted a significant downward trend in 30-day mortality following palliative SACT over an 11-year period. A multicentre study should be carried out to define a more reliable benchmark for this improved indicator.

Conflicts of Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2022.03.015.

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