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ORIGINAL RESEARCH

The Validity of a New Procedure-Based Definition of Cancer Status in Patients with Breast-, Lung- and Colorectal Cancer in the Danish National Patient Registry

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Background/Aim: The Danish National Patient Registry (DNPR) provides unique epidemiological insight, but often lacks granular data. We propose a procedure-based definition of cancer status in patients with breast-, lung- and colorectal cancer, which can be applied to administrative health databases. New definitions of cancer status are needed as mortality and morbidity are closely linked to cancer status, yet most studies only use duration since cancer diagnosis as a severity marker. The aim of the study was to validate a new pragmatic definition.

Methods: Medical journals of 600 patients, with breast-, lung- and colorectal cancer from the Department of Oncology at Herlev-Gentofte Hospital were retrospectively reviewed. We defined active cancer as a cancer diagnosis, not followed by a potentially curative procedure within 6 months of the diagnosis. The remaining patients were characterized as having non-active cancer. This dichotomization was then compared to a cancer status assessment based on treatment received and paraclinical test such as their first post-procedural control scan. Based on this comparison, we calculated the positive predictive value (PPV) of our definitions of active and non-active cancer.

Results: The calculated PPVs for active breast-, lung- and colorectal cancer were 87% (CI 95%: 0.74–0.99), 91% (CI 95%: 0.87–0.96) and 82% (CI 95%: 0.73–0.91). The PPVs for non-active breast-, lung- and colorectal cancer were 95% (CI 95%: 0.92–0.99), 91% (CI 95%: 0.82–0.99) and 73% (CI 95%: 0.66–0.81), respectively.

Conclusion: We found an overall high PPV for both active and non-active cancer across all three types of cancer.

Keywords: active cancer, non-active cancer, DNPR, validation, epidemiology

Introduction

Cancer is a global health concern which accounts for almost one in six deaths worldwide.[1] Therapeutic improvements have led to increased survival rates resulting in more patients living with cancer and consequently patients with cancer constitute an increasingly larger subgroup of patients with other medical conditions.[2] This is interesting because patients with cancer are often considered a homogeneous group when included as a concomitant disease by non-oncological researchers.[3] A recent study shows increased risk of in-hospital mortality and complications depending on cancer type and whether the patient had active cancer or a history of cancer.[4] This emphasizes the need to differentiate between active cancer and historical cancer, when assessing the impact of cancer as a comorbidity. For example, the prognosis of acute coronary syndrome was recently found to vary with cancer type and cancer status[5] which could affect planned non-

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cancer treatments. We propose a procedure-based definition of active cancer and non-active cancer among patients with the three major cancer types: Breast-, lung- and colorectal cancer. Our definition is necessary due to the lack of comprehensive standardized databases, which limits the potential for risk stratification among patients with cancer. We conducted a validation study to examine the positive predictive value (PPV) for our definition of active cancer and non-active cancer in the Danish National Patient Registry.

Materials and Methods

Study Population

The validation study was conducted in Denmark at Herlev-Gentofte Hospital among patients with breast-, lung- and colorectal cancer. Denmark is divided into five regions with considerable homogeneity across all regions, when it comes to sociodemographic and health-related characteristics.[6] Furthermore, national guidelines concerning cancer treatment and diagnostics ensure uniform treatment across all regional hospitals.[7,8] Random extraction of patients was made using R (version 4.0.3 for Mac, R Foundation for Statistical Computing). All patients were from the department of Oncology at Herlev-Gentofte Hospital and were diagnosed with breast-, lung- or colorectal cancer between January 1, 2017, and January 31, 2020. Patients were included at the time of their diagnosis and were based on chart reviews categorized into two groups according to cancer status: Active cancer and non-active cancer. We included 600 patients (200 patients with either breast-, lung- or colorectal cancer) for further analysis. 195 of the randomly extracted patients were not included as control scans were unavailable either because scans had not yet been performed or they fell outside the study period.

Definition of Active Cancer and Non-Active Cancer

Active cancer was defined as a cancer diagnosis not followed by a potentially curative procedure 6 months from the date of diagnosis. The procedures were all surgical procedures, such as mastectomies, except for curative intended stereotactic body radiation therapy (SBRT) given to patients with lung cancer. Non-active cancer was defined as a cancer diagnosis, followed by a potentially curative procedure within 6 months of the diagnosis (see Supplementary Figure 1A and B for definition of cancer status). The 6-month threshold was chosen since we assume any candidate for curative intended treatment will receive it within 6 months regardless of neoadjuvant treatment. In line with current practice,[9–12] procedures we defined as curative depended on the cancer type. The distribution of the used procedures can be seen in Supplementary Figure 2A–C and full list of ICD-10 codes and NOMESCO codes used can be found in Supplementary Table 1. Identification of cancer type and the date of diagnosis were based on a histological description, imaging, or invasive procedures.

Medical Record Review

When determining whether a given procedure was curative, we reviewed the first imaging immediately following the procedure. If the radiologist described no remains of the primary tumor or any metastasis, the patient was classified as having non-active cancer. If the scans were inconclusive, we reviewed the following control scans, biopsies, and medical charts. This approach was applied to both the procedures we expected to be curative and the ones not on our list of potentially curative procedures including concomitant chemoradiotherapy given to patients with lung cancer.

Patients with lung cancer who received SBRT or concomitant chemoradiotherapy were reviewed slightly different due to having necrotic tumor remains. After their treatment regimen ended, we reviewed the first following scan, but accepted stationary tumor status or shrinking tumor remains for patients with localized disease as indicative of a curative treatment.

Patients who did not receive a procedure were identified as having active cancer if they; declined active treatment, received palliative chemotherapy and/or radiotherapy, were referred to a hospice or solely palliative care. We also classified active cancer if patients were discharged with a cancer diagnosis without receiving treatment or having exhausted all treatment options. The medical record reviews were performed by two medical doctors (NN and ML) and one medical student (SKN). Disagreements were resolved by consensus.

Statistical Analysis

The following patient demographics were registered at the time of cancer diagnosis for all patients: age, sex, comorbidities, family history of cancer, alcohol, and tobacco use. Age was described by the median age and the interquartile range (IQR).

We calculated the PPV for active cancer by taking the patients who were determined to have active cancer both by our detection algorithm and the standard evaluation in the form of a medical chart review, divided by the number of patients who according to our algorithm should have active cancer. The sensitivity was calculated as the number of patients who had active cancer confirmed both by our algorithm and the standard evaluation, divided by the total number of patients with active cancer. The PPV for non-active cancer was calculated by taking the patients who were cancer free according to our algorithm and were confirmed cancer free by the standard evaluation, divided by the number of patients who should be cancer free according to our algorithm. See Table 2 for more information on the calculation of the PPVs. We used R (version 4.0.4 for Mac, R Foundation for Statistical Computing) to calculate PPV and corresponding 95% confidence intervals (CI).

Results

Baseline Characteristics

600 patients with either breast-, lung- or colorectal cancer were classified as having either active cancer or non-active cancer based on a review of their charts. The flow-chart of the study cohort is shown in Figure 1. Baseline characteristics are shown in Table 1. The median age for patients with breast cancer was 63 years [IQR: 52–72], 71 years [IQR: 66–76] for patients with lung cancer and 72 years [IQR: 66–79] for patients with colorectal cancer. Patients with lung and colorectal cancers had a higher prevalence of lifestyle risk factors and comorbidities compared to patients with breast cancer (Table 1).

Positive Predictive Values

Sensitivities, specificities and PPVs are shown in Table 2. The calculated PPV for active breast cancer was 87% (CI 95% 0.74–0.99), 91% (CI 95% 0.87–0.96) for active lung cancer and 82% (CI 95% 0.73–0.91) for active colorectal cancer. The PPV for non-active breast was 95% (CI 95% 0.92–0.99), 91% (CI 95% 0.82–0.99) for non-active lung cancer and 73% (CI 95% 0.66–0.81) for non-active colorectal cancer (Table 2).

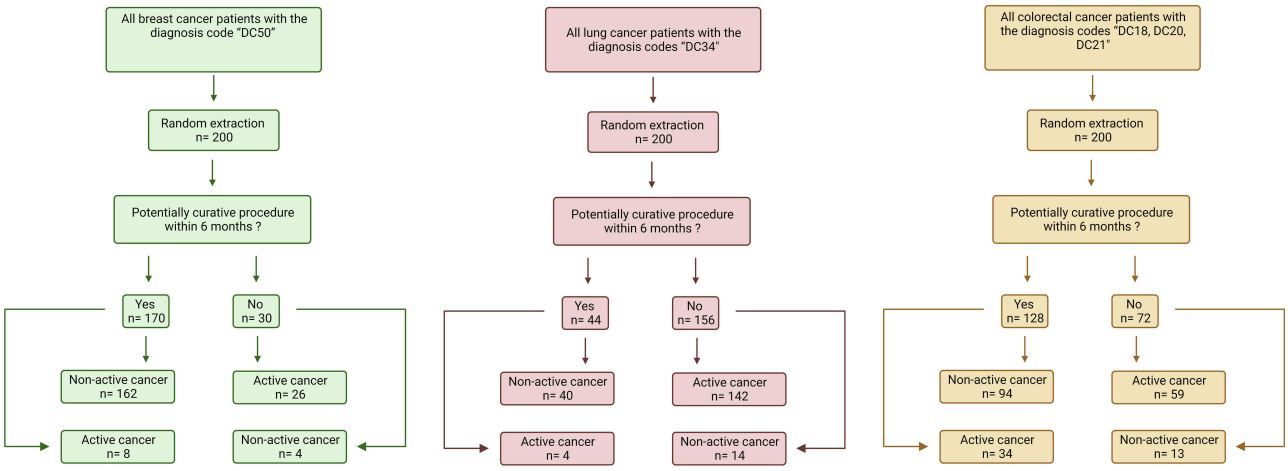

Figure 1 Flowchart of study cohort.
Note: Created with BioRender.com.

Table 1 Baseline Characteristics

	Breast Cancer		Lung Cancer		Colorectal Cancer	
	Active	**Non-Active**	**Active**	**Non-Active**	**Active**	**Non-Active**
Total no. of patients	34	166	146	54	93	107
Age at diagnosis, median [IQR]	76.5 [66.2, 83.0]	61 [52, 69]	71 [67, 77]	70 [64.2, 73.8]	74 [69, 82]	71 [63.5, 77.0]
Gender, male, n %	< 3 (-)	< 3 (-)	69 (47.3)	25 (46.3)	41 (44.1)	61 (57.0)
Lifestyle, n (%)						
Former smoker	8 (23.5)	37 (22.3)	76 (52.1)	26 (48.1)	44 (47.3)	39 (36.4)
Current smoker	3 (8.8)	36 (21.7)	62 (42.5)	25 (46.3)	15 (16.1)	22 (20.6)
Never smoked	16 (47.1)	86 (51.8)	6 (4.1)	3 (5.6)	32 (34.4)	43 (40.2)
Unknown smoking status	7 (20.6)	7 (4.2)	2 (1.4)	< 3 (-)	< 3 (-)	3 (2.8)
No alcohol	14 (41.2)	54 (32.5)	23 (15.8)	< 3 (-)	17 (18.3)	24 (22.4)
Less than 14 units of alcohol	10 (29.4)	94 (56.6)	83 (56.8)	26 (48.1)	57 (61.3)	64 (59.8)
Over 14 units of alcohol	< 3 (-)	6 (3.6)	15 (10.3)	13 (24.1)	14 (15.1)	16 (15.0)
Unknown alcohol consumption	9 (26.5)	12 (7.2)	25 (17.1)	13 (24.1)	5 (5.4)	3 (2.8)
Family history, n (%)						
No family history of cancer	7 (20.6)	53 (31.9)	71 (48.6)	33 (61.1)	34 (36.6)	51 (47.7)
Family history of cancer	5 (14.7)	39 (23.5)	11 (7.5)	5 (9.3)	8 (8.6)	11 (10.3)
Unknown family history	22 (64.7)	74 (44.6)	65 (44.5)	16 (29.6)	51 (54.8)	44 (41.1)
Comorbidities, n, (%)						
No comorbidities	14 (41.2)	93 (56.0)	45 (30.8)	15 (27.8)	25 (26.9)	37 (34.6)
Atrial fibrillation/atrial flutter	< 3 (-)	12 (7.2)	14 (9.6)	6 (11.1)	13 (14.0)	10 (9.3)
AMI	< 3 (-)	< 3 (-)	10 (6.8)	3 (5.6)	6 (6.5)	3 (2.8)
Hypertension	19 (55.9)	52 (31.3)	61 (41.8)	32 (59.3)	42 (45.2)	51 (47.7)
Chronic obstructive pulmonary disease	< 3 (-)	9 (5.4)	32 (21.9)	15 (27.8)	11 (11.8)	6 (5.6)
Peripheral arterial disease	< 3 (-)	< 3 (-)	14 (9.6)	3 (5.6)	< 3 (-)	< 3 (-)
Heart failure	< 3 (-)	< 3 (-)	6 (4.1)	5 (9.3)	7 (7.5)	< 3 (-)
Liver disease	< 3 (-)	3 (1.8)	< 3 (-)	< 3 (-)	3 (3.2)	< 3 (-)
Kidney disease	3 (8.8)	< 3 (-)	8 (5.5)	< 3 (-)	5 (5.4)	3 (2.8)
Hypercholesterolemia	6 (17.6)	36 (21.7)	55 (37.7)	21 (38.9)	43 (46.2)	41 (38.3)
Chronic ischemic heart failure	< 3 (-)	< 3 (-)	17 (11.6)	8 (14.8)	10 (10.8)	9 (8.4)
Diabetes	5 (14.7)	13 (7.8)	25 (17.1)	5 (9.3)	8 (8.6)	12 (11.2)
Venous thromboembolism	< 3 (-)	< 3 (-)	6 (4.1)	< 3 (-)	5 (5.4)	< 3 (-)
Ischemic stroke	< 3 (-)	4 (2.4)	8 (5.5)	< 3 (-)	5 (5.4)	8 (7.5)

(*Continued*)

Table 1 (Continued).

	Breast Cancer		Lung Cancer		Colorectal Cancer	
	Active	Non-Active	Active	Non-Active	Active	Non-Active
Haemorrhagic stroke	< 3 (-)	< 3 (-)	< 3 (-)	< 3 (-)	< 3 (-)	< 3 (-)
Stroke	< 3 (-)	3 (1.8)	5 (3.4)	< 3 (-)	3 (3.2)	7 (6.5)

Table 2 Validity of Active Cancer Definition

	Breast Cancer	Lung Cancer	Colorectal Cancer
Sensitivity = TP/(TP+FN)	26/(26 + 8)≈0.76	142/(142 + 4)≈0.97	59/(59 + 34)≈0.63
Specificity = TN/(FP+TN)	162/(4 + 162)≈0.98	40/(14 + 40)≈0.74	94/(13 + 94)≈0.88
PPV = TP/(TP+FP)	26/(26 + 4)≈0.87	142/(142 + 14)≈0.91	59/(59 + 13)≈0.82
NPV = TN/(FN+TN)	162/(8 +162)≈0.95	40/(4 + 40)≈0.91	94/(34 + 94)≈0.73

Cancer Diagnosis

All patients with breast cancer were diagnosed based on a histological description. Three (1.5%) patients with lung cancer were diagnosed based on their CT scans. Four (2%) patients with colorectal cancer were diagnosed using imaging or invasive procedures. The remaining patients were diagnosed based on histological descriptions.

Identification of Active Cancer

Patients with breast cancer were mainly identified by a combination of palliative chemotherapy and/or radiotherapy (59%), biopsies (17%) and imaging (12%). Patients with lung cancer were diagnosed with active cancer primarily due to receiving palliative chemotherapy and/or radiotherapy (49%) or being referred to palliative care or hospice (31%). Patients with colorectal cancer who had active cancer were mainly identified by imaging (35%) and by continuous treatment with palliative chemotherapy and/or radiotherapy (29%) (Figure 2). Patients who received a potentially curative procedure but still had active

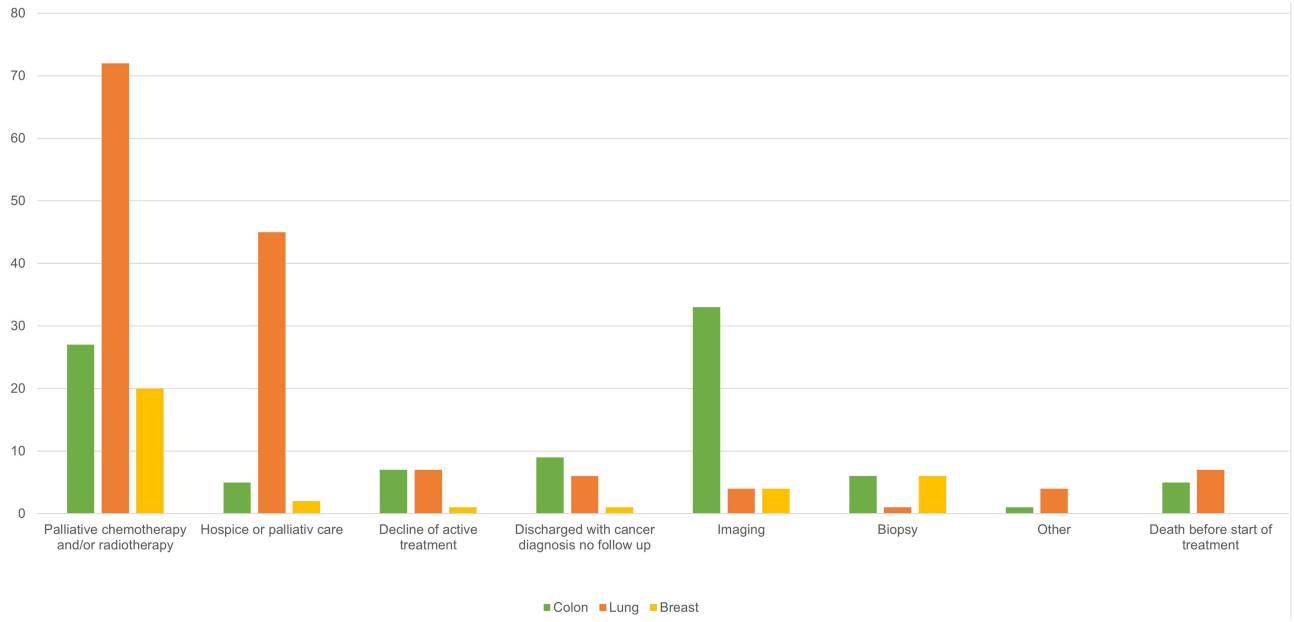

Figure 2 Distribution of active cancer identification method.
Note: Bar chart showing how patients with active cancer were identified during medical chart review.

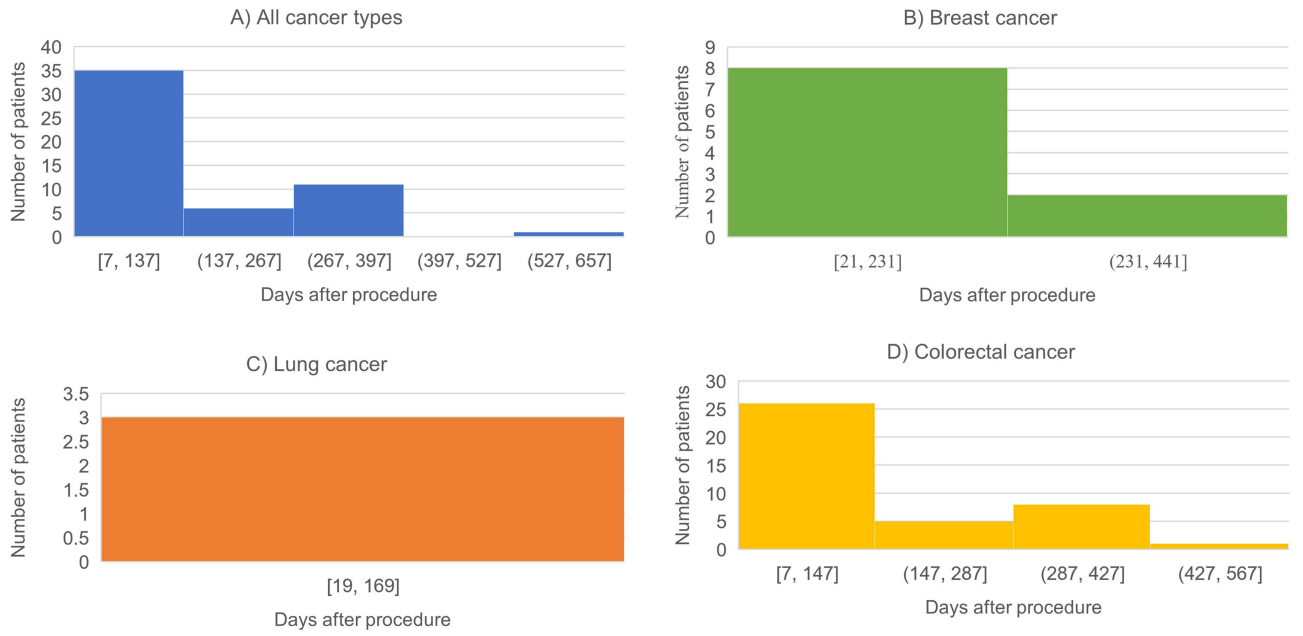

Figure 3 (**A**–**D**) Days after procedure until active cancer diagnosis.
Notes: Histograms showing the number of days after a given patient's potentially curative procedure until their active cancer diagnosis. All cancer types, breast cancer, lung cancer, and colorectal cancer.

cancer, were typically identified within one year after their procedure (Figure 3A–D). Four (2%) patients with colorectal cancer were classified as having non-active cancer based on colonoscopies instead of imaging.

Discussion

In the Danish National Patient Registry, we found high PPVs for active cancer (87% for breast cancer, 91% for lung cancer and 82% for colorectal cancer) and non-active cancer (95% for breast cancer, 91% for lung cancer and 73%, for colorectal cancer) supporting the use of the proposed definitions in epidemiological research.

Notably, in-hospital mortality and surgical complications differ between patients with active cancer and patients with a history of cancer,[4] as does all-cause mortality.[5] No prior studies have assessed the validity of using administrative procedure codes to define active cancer. Previous studies have shown a high PPV regarding colorectal cancer diagnosis and registration in DNPR,[13] as well as cancer diagnosis in general.[14,15] Recent studies have shown high PPVs regarding registration of systemic anticancer treatment in DNPR.[16] Considering this cancer status, systemic anticancer treatment can be incorporated in the future DNPR-based analyses.

Active Cancer and Non-Active Cancer as a Definition

Cancer patients are not typically given a diagnosis of active cancer or non-active cancer by oncologists, which might complicate both treatment strategies in non-oncological settings and research. Currently, the following considerations are made to determine cancer status in the clinical setting: 1) Has the patient received a potentially curative treatment, 2) was the treatment curative, 3) is the treatment ongoing.[17] However, this method is time consuming and requires knowledge of which treatments are potentially curative. Also, it cannot be easily applied to large databases as each patient has to be evaluated individually. Our proposed definition is easily applied to both large databases such as the DNPR, as well as in clinical practice. Similar definitions can be validated and applied to databases such as the Swedish National Patient Registry.

National Guidelines

Our medical review assessment of cancer status largely depended on national guidelines being followed. These are as follows: Patients with colorectal cancer are controlled with a colonoscopy and a CT scan 1 and 3 years after surgery.[18,19]

Patients with lung cancer who receive SBRT or concomitant chemoradiotherapy are controlled with a CT scan every 3 months for 2 years.[20] Patients with breast cancer are controlled with mammograms or ultrasounds between 1 and 2 years after their surgery depending on their age and the type of surgery.[21] These guidelines have not changed during the study period.

Although we only included patients from a single center, we believe our results can be applied on a national scale due to the high degree of adherence to national guidelines regarding cancer treatment and diagnostics.[8,22] Furthermore, our center manages both cancer diagnostics and treatment, both surgical and oncological for the included cancers.

Lung Cancer

We did not include the curative intended concomitant chemoradiotherapy on our list of potentially curative procedures. The reason was in part due to the lack of unambiguous administrative codes. The patients with non-active cancer treated with SBRT are not necessarily disease free, due to how we evaluated the treatment effectiveness.

Strengths and Limitations

Despite the similar PPVs for active and non-active cancer, it is more difficult to diagnose patients with non-active cancer due to the possibility of recurrences. The possible unaccounted-for recurrences lower the certainty of the non-active cancer diagnosis being valid. We are convinced that patients diagnosed with active cancer will not be cured of their cancer since they did not receive a radical procedure, or the procedure was insufficient. As described previously, the control scans we used to determine cancer status took place between 3 months to 2 years after the patients' procedures. A clear control scan is not necessarily indicative of a lifelong absence of cancer. Still, we did not look at later scans to determine cancer status after initial categorization, since we could not identify all cases of recurrent cancer. Our data does suggest recurrences in the short term occur before patients' planned controls, indicating that we have caught most cases of cancer recurrences in the short term (Figure 3A–D). We therefore believe that our PPV accurately takes into account most short-term recurrences. With this in mind, the definition can be used to follow a population with active cancer prospectively and retroactively to see if a patient had active cancer at the time of an event, eg, venous thromboembolism. While caution is advised when following patients with non-active cancer, as inevitably, some will experience a recurrence of cancer.

A major strength of this study was the methodical review of every chart. Almost all patients were diagnosed based on a histological description, and every patient except four patients with colorectal cancer were deemed cancer-free based on imaging. The patients were randomly extracted, and all of them were diagnosed and mainly treated at the same hospital, thereby minimizing selection and inclusion bias.

Not all procedures on our list of potentially curative procedures were used in our sample of patients, limiting what we can infer about the effectiveness of each procedure (Supplementary Figure 2A–C). Finally, we do not account for preoperative/neoadjuvant treatment, eg, anthracyclines even though the choice and long-term outcome of surgical procedures depend on these treatments.[23]

Conclusion

In this validation of register-based definitions of active or non-active cancer, we found an overall high PPV in both groups across all three types of cancer. Using the proposed definitions of cancer status in the DNPR may add more detail in future registry-based studies, for instance, risk stratification among subgroups of cancer patients. Subgroup analyses might highlight how non-cancer treatments can be tailored depending on the patient's cancer type and cancer status.

Ethics

The study was approved by the legal department at Herlev-Gentofte Hospital including directors, and Chief physicians at the Departments of Cardiology and Oncology (Ref. 21022478). Ethical approval in retrospective register-based analysis is not required in Denmark.

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Disclosure

Dr Morten Lamberts reports personal fees from Speaker fee, personal fees from Speaker fee, personal fees from Speaker fee, outside the submitted work. The authors report no other conflicts of interest in this work.

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