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Characteristics of critically ill cancer patients in the Netherlands

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OUTCOMES OF INTENSIVE CARE UNIT ADMISSIONS AFTER ELECTIVE CANCER SURGERY



CHAPTER 4

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Abstract

Background: Postoperative care for major elective cancer surgery is frequently provided on the Intensive Care Unit (ICU).

Objective: To analyze the characteristics and outcome of patients after ICU admission following elective surgery for different cancer diagnoses.

Methods: We analyzed all ICU admissions following elective cancer surgery in the Netherlands collected in the National Intensive Care Evaluation registry between January 2007 and January 2012.

Results: 28,973 patients (9.0.% of all ICU admissions; 40% female) were admitted to the ICU after elective cancer surgery. Of these admissions 77% were planned; in 23% of cases the decision for ICU admission was made during or directly after surgery. The most frequent malignancies were colorectal cancer (25.6%), lung cancer (18.5%) and tumors of the central nervous system (14.3%). Mechanical ventilation was necessary in 24.8% of all patients, most frequently after surgery for esophageal (62.5%) and head and neck cancer (50.2%); 20.7% of patients were treated with vasopressors in the acute postoperative phase, in particular after surgery for esophageal cancer (41.8%). The median length of stay on the ICU was 0.9 days (interquartile ranges [IQR] 0.8 – 1.5); surgery for esophageal cancer was associated with the longest ICU length of stay (median 2.0 days) with the largest variation (IQR 1.0 – 4.8 days). ICU mortality was 1.4%; surgery for gastrointestinal cancer was associated with the highest ICU mortality (colorectal cancer 2.2%, pancreatiko-cholangiocarcinoma 2.0%).

Conclusion: Elective cancer surgery represents a significant part of all ICU admissions, with a short length of stay and low mortality.

Introduction

Although more and more potentially curative cancer treatment-strategies are of multidisciplinary nature, surgical removal of the tumor is still a key component. To achieve long term survival aggressive surgical procedures are not unusual, making direct postoperative management a significant aspect of cancer treatment [1, 2]. A subgroup of cancer patients is admitted to the Intensive Care Unit (ICU) for direct postoperative care, which is related to the type of malignancy and the nature and extent of the surgical procedure. As cancer incidence is increasing by age, also elderly patients are now subject to multimodality strategies with curative intent. These patients are more vulnerable to postoperative complications at least in part due to more comorbidity of cardiovascular, pulmonary and/or metabolic origin [3]. As such, there is a need to obtain insight into the incidence and extent of acute complications and into hospital outcomes after major elective cancer surgery requiring postoperative ICU care.

Although many studies have reported on postoperative morbidity and mortality in unselected patient populations [4-8], few previous investigations examined the specific characteristics of cancer patients in the ICU after major elective surgery. In a large observational study evaluating the outcomes of 88,504 surgical patients admitted to the ICU in Austria during an 11-year period, 9.8% were reported to have a malignant non-metastatic process as comorbid condition [8]. Of these, a total of 6,987 patients were admitted to the ICU after elective surgery. ICU and hospital mortality of all surgical patients were 7.6% and 11.8% respectively; logistic regression analysis identified non-metastatic cancer as an independent risk factor for postoperative hospital mortality (odds ratio 1.20), but this analysis did not discriminate between elective and emergency surgery or different types of surgical procedures [8]. Of importance, whereas postoperative mortality of elective cancer surgery has been the topic of many investigations, none specifically addressed postoperative care on the ICU in this patient group [9-15].

Considering the limited data on postoperative care of cancer patients in the ICU published to date, we here sought to analyze the characteristics and outcome of patients after ICU admission following elective cancer surgery. For this we analyzed all ICU admissions in the Netherlands collected in the National Intensive Care Evaluation (NICE) registry [16] from January 2007 through January 2012 and extracted data from all elective surgical cancer patients.

Patients and Methods

Patient data and selection

The database of the Dutch National Intensive Care Evaluation (NICE) registry was used in this observational study [16]. The participating ICUs provide information on all ICU admissions. For each ICU admission variables are collected that among others describe patient characteristics, severity of illness and acute comorbidities during the first 24 hours of ICU admission, and the ICU and in-hospital mortality and length of stay. The data are encrypted such that all patient-identifying information are untraceable. Since 2007 the recorded variables were used to calculate probabilities of death for each patient using the Acute Physiology and Chronic Health Evaluation (APACHE) IV prognostic model [17]. Data for the current study were collected from all consecutive admissions to 80 ICUs between January 2007 and January 2012. Patients for the present analysis were identified as having been subjected to elective surgery and having an APACHE IV reason for admission containing the term cancer, neoplasm or malignancy. ICU ad-

mission after surgery was recorded as planned (as a consequence of the nature and/or extent of the surgical procedure) or unplanned (following unanticipated perioperative complications).

Ethics

The NICE initiative is officially registered according to the Dutch Personal Data Protection Act. The need for ethical committee approval is waived by the Central Committee on Research Involving Human Subjects, because the study was purely observational and because only anonymous patient data were used.

Netherlands Cancer Registry

Data on the total number of cancer diagnoses in the Netherlands in 2007 to 2010 were obtained from the Netherlands Cancer Registry [18]; patient numbers were divided by 4 to obtain average annual numbers. To relate these numbers to the number of patients admitted to Dutch ICUs after elective cancer surgery, total patient numbers registered within NICE in 2007 to 2011 were divided by 5 to obtain average annual numbers and subsequently multiplied by 1.25 (considering that approximately 80% of all ICU's in the Netherlands participate in NICE).

Statistical analysis

Categorical variables are presented as percentages and continuous variables are presented as mean and standard deviation (SD), or in case of non-normally distributed variables as median and interquartile range (IQR). Standardized mortality ratios (SMRs) were calculated by dividing the actual in-hospital mortality by the expected mortality as calculated by the APACHE IV prognostic model. The SMR is a mortality outcome indicator wherein a SMR above the 1 indicates that mortality is higher than expected based on case-mix and a SMR below the 1 indicates that mortality is lower than expected.

Type of malignancy and outcome: to assess the associations between the type of malignancy and in-hospital mortality multivariate logistic regression analyses were performed. In order to adjust for underlying case-mix differences, the APACHE IV severity of illness score (consisting of the APACHE IV acute physiology score (APS) and comorbidities), age, and gender were included in the model as covariates [17, 19]. The two continuous nonlinear covariates (i.e. age and APACHE IV score) were included in the model using natural cubic regression splines. Regression splines allow accurate estimation of a nonlinear relationship between a covariate and an outcome variable. By univariate analyses, the number of knots (degrees of freedom) per spline was defined using the likelihood ratio test comparing linear, quadratic, cubic and higher-order splines. The resulting spline transformation orders were subsequently used in the final regression analysis.

Trends in mortality: to assess the associations between the period of admission (in trimesters during the study period) and in-hospital mortality, again multivariate logistic regression analyses were performed. In-hospital mortality was the dependent variable and the trimester of admission per year the independent variable. In order to adjust for underlying case-mix differences, the APACHE IV severity of illness score, age, and gender were included in the model as covariate [17, 19]. The two continuous nonlinear covariates were again modeled using natural cubic regression splines.

Trends in length of stay: to assess the associations between the period of admission (in trimesters during the study period) and ICU length of stay, multivariate linear regression

analyses were performed. The ICU length of stay calculated as fractional days based on ICU admission date and time and ICU discharge date and time was the dependent variable and the trimester of admission per year the independent variable. We used the natural logarithm of length of stay because the distribution of length of stay was skewed to the right towards the longest length of stay. In order to adjust for underlying case-mix differences, the APACHE IV severity of illness score, age, and gender were included in the model as covariate [17, 19]. The two continuous nonlinear covariates were again modeled using natural cubic regression splines. For trends analyses we included only those ICUs that participated during the entire study period, i.e. between 2007 and 2012.

According to the APACHE IV exclusion criteria, patients younger than 16 years, patients whose ICU stay was less than 4 hours, patients who were admitted from or discharged to another ICU, patients with burns and, except for hepatic and renal transplantation, patients admitted after transplant operations were excluded for the multivariate logistic regression analyses and the calculation of SMRs [17]. Results were considered statistically significant if p-values were below 0.05. All statistical analyses were performed using PASW statistics 18 (SPSS, Chicago) and R 2.13.0.

Results

Patients

321,493 patients were admitted to the participating ICUs between January 2007 and January 2012. Of these, 28,973 patients (9.0%) were admitted after a planned surgical procedure for cancer (Table 1). Overall, 77% of ICU admissions after elective cancer surgery were planned before the start of surgery; in 23% of cases the decision for ICU admission was made during or directly after surgery. The most frequent operated malignancies were colorectal carcinoma, followed by lung carcinoma and tumors of the central nervous system. Patients admitted to the ICU after colorectal surgery were relatively old (median age 74 years), whereas patients operated for central nervous system tumors were relatively young (median age 57 years); patients admitted to the ICU for postoperative care for other types of cancer surgery were within the same age range (median age between 64 and 68 years). In all patient groups the most prevalent chronic comorbidities were diabetes and chronic obstructive pulmonary disease. Diabetes was most prevalent in patients undergoing surgery for pancreatic and cholangiocarcinoma, whereas chronic obstructive pulmonary disease was most prevalent in patients admitted after surgery for lung carcinoma. Almost one tenth of patients were considered immune compromised based on use of immune suppressive medication and/or receipt of chemotherapy or radiation therapy in the year before ICU admission.

Acute postoperative morbidity and care

Table 2 lists acute postoperative events on the ICU in all patient groups. Almost one in four patients received mechanical ventilation postoperatively. Surgical procedures that required mechanical ventilation in the acute postoperative phase most frequently were operations for esophageal cancer and head and neck cancer. One of five patients was treated with vasopressors in the acute postoperative phase, in particular patients after surgery for esophageal cancer. Cardiac dysrhythmia was the most frequent postoperative comorbidity. Infections were relatively rare; these were most prevalent in patients after surgery for gastrointestinal cancer.

¹ Includes surgery for prostate cancer, testicular cancer (<3% of all patients in this group)

² Includes surgery for breast cancer, ovarian cancer, endometrial cancer, cervical cancer, vaginal cancer

Table 2: Morbidity, mortality and length of stay

	All patients	Colorectal cancer surgery	Thoracotomy for lung cancer	Central Nervous System surgery for neoplasm	Bladder cancer surgery	Esophageal cancer surgery	Renal cancer surgery	Pancreatico-cholangio-cancer surgery	Head and Neck cancer surgery	Female cancer surgery	Male cancer surgery	Other types of cancer
Number of patients	28,973	7,404	5,358	4,157	2,261	2,017	1,348	987	888	707	592	3,254
Acute comorbidity¹ (%)												
Confirmed infection	2.1	3.3	1.5	0.4	1.3	2.8	2.2	3.3	1.8	1.7	2.0	1.9
Pneumonia	0.5	0.8	0.5	0.1	0.2	0.9	0.5	0.4	0.9	0.1	0.2	0.5
Sepsis	0.7	1.3	0.2	0.0	0.9	0.6	0.7	1.9	0.3	1.0	1.0	0.5
Cardiac dysrhythmia	3.0	5.0	2.5	1.4	1.9	2.9	4.3	2.0	1.5	2.7	4.6	2.4
Acute renal failure	1.2	1.6	0.4	0.1	1.6	0.6	5.0	1.2	0.2	2.8	1.4	1.2
Mechanical ventilation	24.8	22.1	12.5	23.1	18.2	62.5	21.8	35.1	50.2	15.7	23.8	27.6
Vasopressors	20.7	25.7	12.6	7.5	23.5	41.8	23.5	23.5	19.0	17.3	25.0	22.7
APACHE IV score												
Mean	44.3	50.1	41.0	33.6	45.7	46.5	48.6	49.5	42.4	42.9	46.8	45.3
Standard Deviation	18.5	19.5	15.3	17.2	16.0	17.2	19.0	19.6	16.2	17.2	18.1	18.3
ICU length of stay (days)												
Median	0.9	0.9	0.9	0.9	0.9	2.0	0.9	0.9	0.9	0.9	0.9	0.9
Interquartile Ranges	0.8-1.5	0.8-1.8	0.8-1.0	0.8-0.9	0.8-1.0	1.0-4.8	0.8-1.2	0.8-1.9	0.7-1.7	0.8-1.0	0.8-1.1	0.8-1.7
Hospital length of stay (days)												
Median	12	13	10	8	16	15	9	17	17	7	9	12
Interquartile Ranges	8-19	9-22	8-14	6-12	13-22	11-24	7-14	12-28	11-25	5-13	6-16	8-19
Mortality												
ICU (%)	1.4	2.2	0.8	0.7	0.5	1.8	1.2	2.0	1.0	0.8	1.3	1.9
Hospital (%)	4.7	8.0	3.0	2.2	2.9	5.0	3.8	7.6	3.3	1.5	3.0	5.6
APACHE IV SMR ²	0.7	0.7	0.5	0.6	1.3	0.5	1.2	0.7	1.1	0.6	0.6	0.6
95% Confidence Interval	0.6-0.7	0.6-0.8	0.4-0.6	0.5-0.8	1.0-1.6	0.4-0.7	0.9-1.5	0.6-0.9	0.7-1.6	0.3-1.1	0.3-0.9	0.6-0.7

¹ Registered within 24 hours of admission

² Standardized Mortality Ratio

Table 3: Mortality risk by type of cancer surgery (multivariate analysis)

	Odds ratio (SD) ¹	<i>Odds ratio for mortality risk by type of cancer surgery as compared with cancer patients with other types of surgery. Multivariate analysis including age, gender and APACHE IV score. * P < 0.05. ¹Standard Deviation</i>
Colorectal cancer surgery	1.41 (1.23-1.60) *	
Thoracotomy for lung cancer	0.82 (0.69-0.98) *	
Central Nervous System surgery for neoplasm	0.86 (0.68-1.09)	
Bladder cancer surgery	0.57 (0.44-0.74) *	
Esophageal cancer surgery	1.14 (0.91-1.43)	
Renal cancer surgery	0.61 (0.45-0.83) *	
Pancreatic - Cholangio cancer surgery	1.60 (1.20-2.04) *	
Head and Neck cancer surgery	0.84 (0.56-1.26)	
Female cancer surgery	0.60 (0.36-1.01)	
Male cancer surgery	0.27 (0.14-0.53) *	
Other types of cancer	1.24 (1.03-1.47) *	

Length of stay and mortality

Table 2 lists ICU and hospital lengths of stay and mortality in all patient groups. The median length of stay on the ICU for the entire patient group was 0.9 days; surgery for esophageal carcinoma was associated with the longest ICU length of stay (median 2.0 days) and with the largest variation. The median hospital length of stay was 12.0 days for all patients combined; patients stayed in the hospital longest after surgery for pancreatico-cholangiocarcinoma, head and neck cancer and bladder cancer. Patients whose ICU admission was not already planned at the start of surgery had a slightly longer ICU length of stay (0.94 days (IQR 0.79 – 1.98 days) vs. 0.90 days (IQR 0.79 – 1.10 days) in planned patients) ($P < 0.01$). For all patient groups combined ICU and hospital mortalities were 1.4% and 4.7% respectively. Surgery for gastrointestinal cancer was associated with the highest ICU and hospital mortality. In accordance, multivariate logistic regression analysis assessing the associations between the type of malignancy and in-hospital mortality showed that surgery for pancreatico-cholangiocarcinoma (OR 1.56) and colorectal carcinoma (OR 1.41) were associated with a significantly increased risk for mortality (Table 3). SMRs were < 1.0 for most types of cancer surgery (except for bladder cancer, head and neck cancer, and male cancer surgery), indicating a lower mortality than expected based on the APACHE IV prognostic model (Table 3).

Trends in length of stay and mortality

We performed multivariate linear regression analysis to assess the associations between the period of admission (in trimesters) and ICU length of stay; for this analysis we studied the main four surgical categories and only included the 46 ICUs that participated during the entire five-year study period. ICU length of stay changed only modestly over time for all patients undergoing cancer surgery combined and when divided in surgical procedures by organ system (data not shown). In contrast, hospital mortality showed a significant decrease in time (from 5.7% in 2007 to 4.1% in 2011, $P < 0.05$; Figure 1). When analyzed for different types of cancer surgery, only hospital mortality after surgery for gastrointestinal cancer (but not for lung or urinary tract cancer) demonstrated a significant decline in time (from 8.0% in 2007 to 5.2% in 2011, $P < 0.05$; Figure 1).

Table 4: Annual number of patients per cancer diagnosis and proportion admitted to the ICU

	Average number of patients per year diagnosed with different types of cancer in the Netherlands between 2007-2010 (ref. 18)	Patients admitted to the ICU for post-operative care per year (%) ¹
Colorectal Cancer	12,296	1,851 (15.1)
Lung Cancer	11,612	1,340 (11.5)
Central Nervous System Neoplasm	1,167	1,039 (89.0)
Bladder Cancer	3,208	565 (17.6)
Esophageal Cancer	2,403	504 (20.1)
Renal Cancer	2,079	337 (16.2)
Pancreatic - Cholangio Cancer	2,520	247 (9.8)
Head and Neck Cancer	2,815	222 (7.9)
Female Cancer	4,362	148 (3.4)
Male Cancer	10,838	177 (1.6)
All types of cancer	91,428	7,243 (7.9)

¹ Based on 80% of the ICU-beds participating in the NICE registry

Total number of cancer diagnoses in the Netherlands during study period

To obtain insight in the proportion of patients per cancer diagnosis admitted to the ICU after elective surgery, we analyzed data provided by the Netherlands Cancer Registry. Table 4 lists the total number of cancer diagnoses registered herein during the study period (2007-2010). Furthermore, Table 4 shows estimates of the proportion of patients diagnosed with cancer in the Netherlands that was admitted to the ICU after elective surgery, stratified according to the type of malignancy.

Discussion

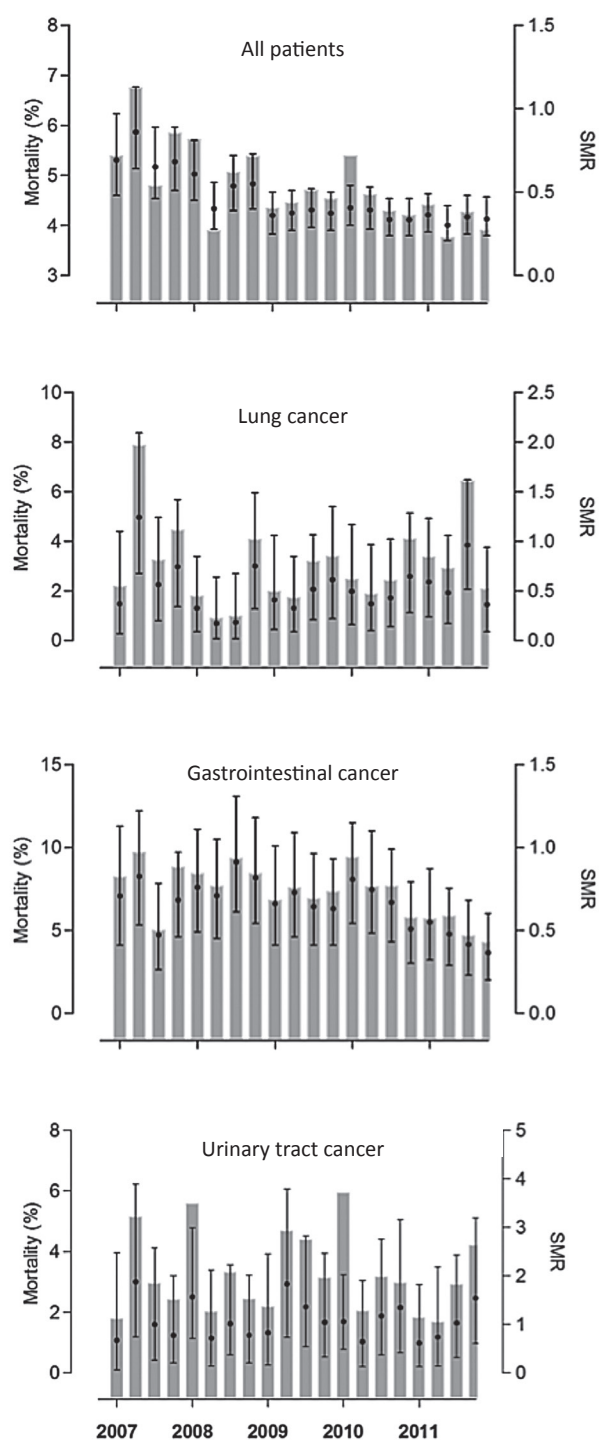
Background and main results

Knowledge of the specific characteristics of cancer patients in the ICU after major elective surgery is limited. As a consequence of advances in cancer treatment, ICU physicians can be expected to be confronted with increasing numbers of oncology patients directly following aggressive surgical treatments. Surgical procedures for different malignancies vary considerably, each carrying their own specific risks during the acute postoperative care.

This study focused on the acute postoperative ICU care and morbidity after major elective cancer surgery. Our survey comprised 28,973 elective surgical cancer patients admitted to 80 ICUs during a five-year period, providing information on acute morbidity, as well as ICU and hospital length of stay and mortality across distinct cancer diagnoses. These patients represented 9.0% of all ICU admissions (Table 1) and approximately 16% of all surgical and 22% of all elective surgical admissions (data not shown). Overall, ICU length of stay was short (median 0.9

Figure 1: Hospital mortality and standardized mortality ratios per quartile from January 2007 to January 2012

Hospital mortality is shown as percentage of the total number of patients within that category (left X axis). Standardized mortality ratios (SMR) are shown as medians with 95% confidence intervals (right X axis). Data are shown for all cancer patients undergoing elective surgery and for patients operated for lung cancer, gastrointestinal cancer (colorectal, esophageal and pancreatico-cholangio cancer) or urinary tract cancer (renal and bladder cancer). Hospital mortality and SMR's amongst all cancer patients combined showed significant decreases in time ($P < 0.05$); when analyzed for different types of cancer surgery, only hospital mortality and SMR's after surgery for gastrointestinal cancer (but not for lung or urinary tract cancer) demonstrated significant declines in time ($P < 0.05$).



days) with mechanical ventilation (one of four patients) and vasopressor use (one of five patients) as the most prevalent supportive measures. ICU and hospital mortality were 1.4% and 4.7% respectively. During the study period hospital mortality showed a significant decrease in time from 5.7% in 2007 to 4.1% in 2011.

Previous studies reporting on cancer patients in the ICU

The current study used data from the Dutch National Intensive Care Evaluation (NICE) database to obtain insight in the epidemiology and short-term outcome of cancer patients admitted to general ICUs after elective cancer surgery. Although knowledge of long-term outcomes of cancer surgery is essential, awareness of the facts on the duration of ICU admission, comorbidity and mortality in the ICU after major elective operations for malignancies is important for optimal delivery of acute care and in light of the high costs of the use of ICU amenities. Most patients in this analysis left the ICU within a day, with patients operated for esophageal cancer as the only exception (median ICU length of stay 2 days with a large interindividual variation). Several earlier studies reported on the outcome of cancer patients in the ICU [20]. One investigation specifically addressed cancer patients admitted to the ICU after elective surgery; this study encompassed 381 patients who had a median length of stay on the ICU of 2 days and an ICU mortality of 6% [1]. This relatively small study is difficult to compare with our current results since the type of surgery was not specified.

Estimation of proportion of patients per cancer diagnosis admitted to ICU after elective surgery

One of four patients admitted to the ICU after elective cancer surgery was operated for colorectal carcinoma. This patient group had the highest ICU and hospital mortality (2.2% and 8.0% respectively). Our investigation does not provide insight into how many patients were operated for colorectal carcinoma in total. Indeed, many patients are transferred to a general surgical ward after elective colorectal cancer surgery. Comparing data from the Netherlands Cancer Registry, which provides data on all new cancer diagnoses in the country [18], with the data from the NICE registry, we estimate that approximately 15% of all patients with colorectal carcinoma were admitted to the ICU after surgery (considering that approximately 80% of all ICU beds in the Netherlands are included in the NICE registry); the remaining 85% of patients was either not operated or received postoperative care outside the ICU. Lung cancer was the second most prevalent diagnosis in our elective surgical ICU cohort; the ICU and hospital mortality of this group was relatively low (0.8% and 3.0% respectively). Based on data from the Netherlands Cancer Registry [18], we estimate [18] that 12% of all patients with this malignancy (irrespective of type of therapy) received ICU care after surgery. Along the same lines, the percentage of all patients diagnosed with a specific cancer that is admitted to the ICU after elective surgery can be estimated: esophageal cancer 21%, pancreatic-cholangiocarcinoma 12%, renal carcinoma 16%, bladder cancer 20%, male cancer 8%, female cancer 4%, head and neck cancer 80% and CNS tumors 89%. Altogether, these estimates demonstrate that many cancer patients receive postoperative ICU care and emphasize the importance of analyzing clinical outcome data of ICU admissions after cancer surgery.

Limitations

Our study has several limitations. The present study specifically focused on the epidemiology and short-term outcome of cancer patients admitted to general ICUs after elective cancer

surgery. Thus, this survey involves a selected population and does not provide information on in-hospital outcomes of cancer patients who were not admitted to the ICU postoperatively. Our study has several limitations. The present study specifically focused on the epidemiology and short-term outcome of cancer patients admitted to general ICUs after elective cancer surgery. The decision to electively admit these patients to the ICU is subjective. Major differences in the indications for post-operative ICU care after cancer surgery may exist between different hospitals and may influence outcome. Follow up of our patients was limited to hospital discharge; we cannot exclude that some patients may have died soon after hospital discharge. Moreover, NICE does not contain data on the stage of cancer and/or details about previous cancer treatments; this is caused by the fact that data collection within the NICE registry does not focus specifically on cancer patients. Finally, information about specific postoperative complications, such as thrombosis and bleeding, is not available.

Hospital mortality

In our cohort of patients who required postoperative care in the ICU, hospital mortality was 4.7%, a percentage that significantly decreased in time from 2007 to 2012. For the majority of different types of cancer surgeries, hospital mortality rates were in the same range as published previously for patients subjected to elective surgery for cancer of the lung [21], esophagus [22, 23], pancreas [24], female genital tract [25], bladder [26] and head and neck [27, 28]. In contrast, hospital mortality amongst patients with colorectal carcinoma was higher than reported earlier for elective surgery in this group [9, 29, 30], which can be explained, at least in part, by the fact that patients selected for postoperative ICU care likely represent a high-risk subgroup. In addition, in a relatively high proportion of this group ICU admission was not planned prior to surgery (in 32% of cases), indicative of unanticipated perioperative complications. Moreover, the median age was high (74 years) in our cohort of patients with colorectal carcinoma and postoperative mortality after colorectal surgery is known to increase with age [31].

Conclusion

This multicenter five-year observational study conducted in 80 general ICUs shows that the most frequent cancer types admitted to the ICU after elective surgery are colorectal carcinoma, lung carcinoma and head and neck carcinoma. The median length of stay in the ICU was less than one day for almost all cancers, while postoperative care for esophageal carcinoma typically is longer (median two days). In addition, overall ICU mortality was low in this patient population, with highest mortality (2.2%) found in patients operated for esophageal carcinoma. The present study is the first to report on acute care, morbidities and outcome of admissions to general ICUs after major elective cancer surgery, revealing that the vast majority of patients demonstrate a favorable outcome.

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