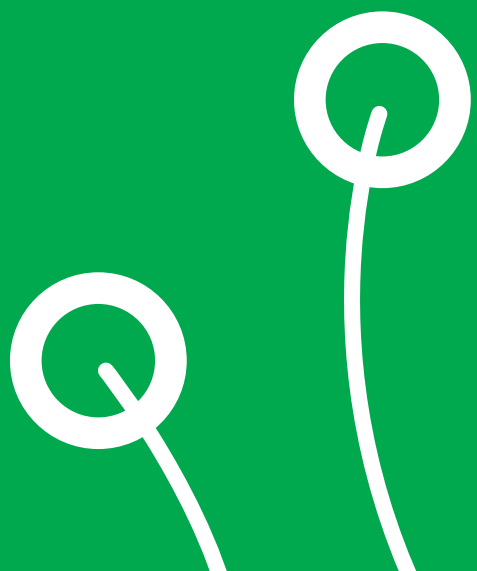
CHARACTERISTICS OF CRITICALLY ILL CANCER PATIENTS IN THE NETHERLANDS

MONIQUE M.E.M. BOS



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geboren te Heeze in 1961

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	Prof. Dr. R.A.E.M. Tollenaar
	Dr. S. Zweegman (Vrije Universiteit Amsterdam)

"…just do the right thing…"

Stephen F. Lowry (1949-2011)

Professor and Chair of the Department of Surgery
Robert Wood Johnson Medical School
New Brunswick, NJ, USA

Voor **Tom, Helen en Lara**
Aan **…de bosjes…**

CONTENTS

INTRODUCTION

CHAPTER 1

Monique M.E.M. Bos

Based in part on:
Patients with cancer on the ICU: the times they are changing
Evert de Jonge & Monique M.E.M. Bos
Critical Care 2009; 13: 122

Background

Advances in the diagnosis and therapy of cancer have led to improved prognoses and extension of survival time in patients with a malignancy [1]. Such progress, however, has involved aggressive therapy and support. As a consequence, patients with a malignancy more frequently encounter acute complications resulting in critical illness during the course of their disease and an increasingly large proportion of these patients require admission to an intensive care unit (ICU). This thesis studies the epidemiology and outcome of critical illness arising as an acute complication of cancer and/or its treatment.

Cancer and Intensive Care

Admission of cancer patients to the ICU was once considered inappropriate because their long-term prognosis was perceived to be poor as a consequence of their underlying disease. In 1999, in guidelines for ICU admission, a taskforce of the American College of Critical Care Medicine concluded that patients with hematological or metastasized solid malignancies were poor candidates for ICU admission [2]. These patients were considered to have a very high risk (up to 90%) of mortality. At that time, immediate treatment limitations or even refusal of ICU admission for these patients were advocated [3]. Over the past few decades, however, significant strides have been made in reducing the overall mortality from cancer while simultaneously improving the quality of life of survivors.

Recent studies reported that patients with a malignancy represent a large proportion of ICU patients. The SAPS-3 study, performed in an international population comprising almost 20,000 ICU patients, showed that 3% of these patients had metastatic cancer, 6% had non-metastatic cancer and 2% had hematological cancer [4]. Similarly, in a substudy from the Sepsis Occurrence in Acutely Ill Patients (SOAP) study conducted in 198 European ICUs, 15% of patients had a malignancy, mostly solid tumors but also hematological malignancies [5]. Importantly, this latter study reported a hospital mortality of 58% in ICU patients with hematological cancer and 27% in patients with solid malignancies, compared with 23% in ICU patients without cancer [5]. In a Brazilian study involving 1,090 patients with cancer requiring ICU admission for reasons other than routine postoperative care, hospital mortality was 51% and 6-month mortality was 61%; most of these patients had non-metastasized solid cancer, and most patients required mechanical ventilation [6]. In an investigation that analyzed 717 consecutive cancer patients admitted to 28 Brazilian ICUs during a two-month period, overall mortality in cancer patients was 30% [7]. Others have also reported the improvement in prognosis after ICU admission for patients with hematological cancer. In hematopoietic stem cell transplant recipients who received invasive mechanical ventilation, mortality was uniformly higher than 90% in studies before 1993, but gradually decreased to 52% in 2000 [8].

Most patients with cancer enter the ICU for postoperative care. Indeed, in light of the increased life expectancy and advances in cancer treatment, the surgical intensivist is confronted with greater numbers of oncology patients undergoing aggressive surgical treatments with curative intent or for palliation (*e.g.* for alleviating obstruction, infection, bleeding or pain). Although postoperative mortality of elective cancer surgery has been the topic of many investigations, none specifically addressed postoperative care in the ICU in this patient group [9-15]. In a large observational study evaluating the outcomes of 88,504 surgical patients admitted to the ICU in Austria during an 11-year period, non-metastatic cancer was an independent risk factor for postoperative hospital mortality (odds ratio 1.20) [16]. However, this study did

not discriminate between elective and emergency surgery or different types of surgical procedures [16]. One relatively small investigation encompassing 381 cancer patients specifically addressed postoperative ICU care after elective surgery, reporting a median length of stay on the ICU of 2 days and an ICU mortality of 6%; unfortunately, the type of surgery was not specified [7]. Particular subgroups of cancer patients are more likely to need acute surgery during their disease. In this respect patients with colorectal cancer stand out: a recent report even suggested that one in four cases of bowel cancer are diagnosed only after emergency admission to the hospital [17]. At present, however, little is known about postoperative ICU care in these patients. Clearly, there is a lack of knowledge on the outcome of cancer patients admitted to the ICU after elective or emergency surgery.

Together, these data show that ICU treatment is not futile for all patients with cancer. Hence, there is a need to increase our knowledge on the outcome of cancer patients in the ICU and to raise awareness amongst oncologists and intensive care physicians regarding the improved prognosis of patients with malignancy in need for ICU care.

Infections in cancer patients

Cancer patients are more susceptible to infection and infections are a major cause of prolonged hospitalization in patients who have cancer [18]. This increased infection risk at least in part is the consequence of aggressive cancer therapies resulting in disruption of mucosal barriers, neutropenia, cellular and humoral immune dysfunction, splenectomy and/or the presence of indwelling vascular catheters. In addition, local tumor effects contribute to the increased vulnerability for infection; the source of infection is often related to the anatomic site of the primary tumor, e.g. patients with lung cancer more commonly acquire pneumonia, whereas patients with prostate cancer more often encounter genitourinary infections [18]. Organisms that cause infections in cancer patients span the entire range from bacteria, viruses, fungi to protozoa. Importantly, infections by microorganisms with low virulence can result in significant morbidity and mortality in patients with cancer [19, 20].

The most severe clinical manifestation of infection is sepsis, defined as the detrimental response of the host to invading pathogens. Patients with cancer are ten times more likely to develop sepsis than patients who do not have cancer. Moreover, cancer is associated with a 30% higher risk for death from sepsis and sepsis is responsible for approximately 10% of all cancer deaths [20, 21]. Hematologic malignancies (66.4 per 1000) are more frequently associated with severe sepsis than solid tumors (7.6 per 1000) and have a higher mortality rate [5, 21].

Chemotherapy-induced neutropenia is a clear risk factor to acquire an infection, and infections account for the majority of chemotherapy-associated deaths [22]. In neutropenic patients bacteria are the most common cause of infection and at least 50% of patients with neutropenic fever have bacteremia. Since the 1990s Gram-positive bacteria outnumber Gram-negative organisms, at least in part due to the increasing use of intravascular catheters. Fungi are frequent causes of infections in neutropenic patients who received broad-spectrum antibiotics; other risk factors include prior use of steroids, advanced age, intensity of chemotherapy and the presence of an indwelling central catheter [18]. Fungal infection in patients who are neutropenic is most frequently caused by *Candida* species, followed by *Aspergillus* species.

An important risk factor for infections in cancer patients is the use of central vascular catheters (CVC). Indeed, CVC-related blood stream infections are a major cause of morbidity

and mortality in cancer patients, estimated to occur in 1.0 to 1.9/1,000 catheter days [23]. Catheters can be tunneled (e.g. Hickman, Groshong and Broviac catheters), non-tunneled or implantable (e.g. Port-A-Cath). Non-tunneled CVC infection often originates from extraluminal colonization of the catheter, usually from the skin. In tunneled CVC or implantable devices contamination of the catheter hub and intraluminal infection are the most frequent routes of infection. Common causative organisms in CVC-related blood stream infections include coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic Gram-negative bacilli and *Candida albicans* [18]. Besides by infection, the use of CVCs can be complicated by thrombosis. Septic thrombosis is a serious condition frequently associated with persistent bacteremia or fungemia.

Outline of the thesis

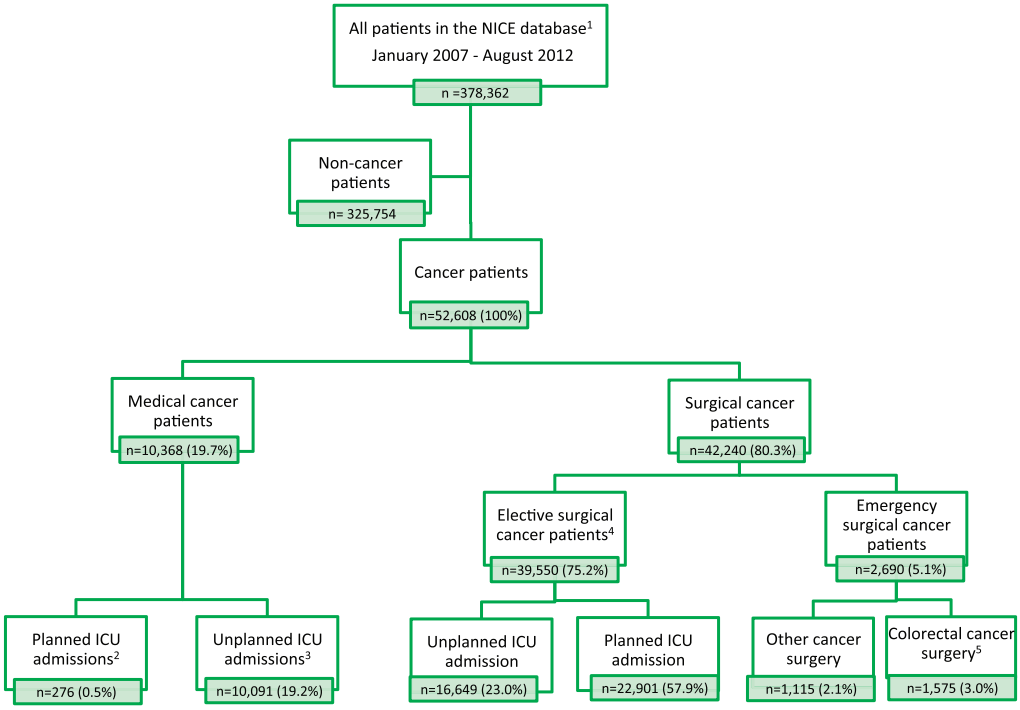
The *general objective* of the research presented in this thesis is to obtain more insight in the occurrence and outcome of acute critical illness in patients with cancer.

Chapter 2 seeks to provide insight into the proportion of cancer patients that requires ICU admission during the course of their disease. For this the patient registration systems of four hospitals is used, containing encoded "Diagnosis Treatment Combinations" (DTC) that specify information about the type of care, diagnosis and treatment; to identify the patients from this primary cohort admitted to an ICU during the 5-year study period (January 2006 – January 2011), encrypted data are linked with the database of the Dutch ***National Intensive Care Evaluation (NICE) registry.***

The NICE registry is also used in Chapters 3-5, to determine the characteristics and outcome of cancer patients admitted to the ICU. In 1996 the NICE foundation started collecting data of patients admitted to Dutch ICUs [24]. The participating ICUs provide information on all ICU admissions with the aim to assess and compare the performance of the ICUs and to improve the quality of care. For each ICU admission variables are collected that describe patient characteristics, severity of illness during the first 24 hours of ICU admission, and the ICU and in-hospital mortality and length of stay. NICE makes use of the Acute Physiology and Chronic Health Evaluation (APACHE) IV scoring system to classify patients according to admission diagnosis and comorbidities [25]. APACHE IV is based on age, chronic health conditions and physiologic data collected on the worst measurement for each component on ICU day 1. Chronic health variables are AIDS, cirrhosis, hepatic failure, immunosuppression, lymphoma, leukemia or myeloma and metastatic tumor. Physiological data include pulse rate, mean blood pressure, temperature, respiratory rate, PaO2/FIO2 ratio (or P(A-a)O2 for intubated patients with FIO2 0.5), hematocrit, white blood cell count, creatinine, urine output, blood urea nitrogen, sodium, albumin, bilirubin, glucose, acid base abnormalities and neurological abnormalities based on Glasgow Coma Score. Besides the APACHE IV score, the Simplified Acute Physiology Score (SAPS) II is used to calculate a score for each patient based on the most abnormal data from the first 24 hours following ICU admission; from this the severity of illness is quantified and the corresponding probability of in-hospital mortality calculated. As an indicator for quality assessment of intensive care, the observed mortality in the ICU population is compared with the calculated case–mix corrected mortality in that population. Each ICU admission diagnosis is first classified as non-operative or postoperative, next by body system or a transplant or trauma-related category, and then by diagnosis selecting one of 430 well defined diseases, injuries, surgical procedures or events that were most immediately threatening to the patient

and required the services of the intensive or coronary care unit. The NICE data definitions are contained in a data dictionary (www.stichtingNICE.nl). At least two physicians per ICU are obliged to attend a central training session organized by the NICE board, during which the data definitions are discussed. Physicians who have attended the central training session subsequently train their local staff. At present, approximately 85% of all Dutch ICUs participate in NICE. In this thesis, NICE data collected between January 2007 and September 2012 are used. *Figure 1* shows the overall population contained within the NICE registry during this period. In total 378,362 patients were admitted to the ICU during this period, of whom 13.9% had cancer.

Figure 1: Patients included in the NICE registry (January 2007 – August 2012) and overview of different cancer subgroups studied in this thesis



[1] All patients admitted to an ICU participating in NICE in the Netherlands between January 2007 and August 2012

[2] Planned medical cancer patients are rare. This group is not included in one of the Chapters of this thesis. Subgroups were hematologic malignancies (n=100), gastro-intestinal cancer (n=52), malignancies of the central nerve system (n=10), lung cancer (n=12), genito-urinary malignancy (n=7), thyroid cancer (n=1), head and neck cancer (n=5), and not further specified i.e. neoplasm non-operative (n=99).

[3] Unplanned medical cancer patients are studied in Chapter 3 (data from January 2007-January 2011)

[4] Planned surgical cancer patients are studied in Chapter 4 (data from January 2007-January 2012)

[5] 58.6% of unplanned surgical cancer patients involve emergency colorectal cancer surgery; these patients are studied in Chapter 5 (data from January 2007 – August 2012).

Chapter 3 focuses on cancer patients with acute (unplanned) admission to the ICU between January 2007 and January 2011, with the aim to compare their characteristics and outcomes with those of critically ill patients without cancer. **Chapter 4** focuses on the outcome of cancer patients admitted to the ICU after major elective surgery between January 2007 and January 2012, stratified according to cancer diagnosis. **Chapter 5** focuses on a subgroup of surgical oncology patients, in particular patients with colorectal cancer admitted to the ICU after emergency colorectal surgery between January 2007 and September 2012; these patients are compared with patients admitted to the ICU after emergency colorectal surgery for non-malignant disease (i.e. diverticular disease, fistula or abscess, gastrointestinal obstruction, perforation or rupture, or peritonitis).

Chapters 6 and 7 describe infectious complications in patients with cancer. **Chapter 6** seeks to compare causative microorganisms in bloodstream infections in patients with or without cancer in a 600-bed teaching community hospital (Reinier de Graaf Hospital). For this all positive blood cultures from adult patients between January 2005 and January 2011 are analyzed. **Chapter 7** presents a retrospective analysis of the indications, duration of use, complications and reasons for removal of Port-A-Caths in cancer patients treated in the Reinier de Graaf Hospital from January 2005 to December 2010, comparing these with findings in patients who received a Port-A-Cath in the same period for reasons not related to cancer.

Chapter 8 (and 9) contains the summary of this thesis, as well as a general discussion and future perspectives.

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INTENSIVE CARE ADMISSION OF CANCER PATIENTS: A COMPARATIVE ANALYSIS

CHAPTER 2

Monique M.E.M. Bos,
Ilona W.M. Verburg,
Ineke Dumaij,
Jacqueline Stouthard,
Johannes W.R. Nortier,
Dick Richel,
Eric P.A. van der Zwan,
Nicolette F. de Keizer and
Evert de Jonge

Abstract

Introduction: Knowledge of the proportion of cancer patients that is admitted to an ICU is limited. The aim of this study was to obtain insight into which proportion of cancer patients is admitted to an ICU and how their survival, demographic and clinical characteristics relate to cancer patients who were not admitted to the ICU.
Methods: Patients registered with a cancer diagnosis between January 1st 2006 and January 1st 2011 were selected from the information systems of four hospitals in the Netherlands. To determine which of these patients were admitted to the ICU their data were linked to the Dutch National Intensive Care Evaluation registry.
Results: 36,860 patients with cancer were identified, of whom 2,374 (6.4%) were admitted to the ICU. Most ICU admissions involved cancers that received only surgical treatment (11.8% of all cancers in the general population). Among different cancer diagnoses, esophageal cancer (27.3%) and other types of gastrointestinal cancer most commonly lead to ICU admission. Although more women (54.0%) than men were registered with cancer, the proportion of male cancer patients admitted to an ICU was much higher (9.3 vs. 4.0%, $p < 0.001$). Long-term survival of cancer patients admitted to the ICU was much lower (median survival time 771 days) than in patients not admitted to the ICU (median survival time not reached, $p < 0.001$). Nonetheless, survival after ICU admission stratified according to cancer diagnosis was substantial.
Conclusion: One out of 16 patients with cancer was admitted to an ICU. Men with cancer had a two-fold higher risk of ICU admission than women with cancer. Although mortality was higher in patients who were admitted to the ICU, our data indicate that intensive care support for patients with cancer should not be considered futile.

Introduction

The prognosis of cancer patients has improved due to earlier diagnosis and better therapeutic options [1]. As a consequence of more aggressive therapies, the need of cancer patients for intensive care unit (ICU) support during the course of their disease has increased [2]. Recent data indicate that the outcome of cancer patients on the ICU has improved significantly [3, 4]. Although once deemed unfitting because of their perceived poor prognosis, ICU admission is now considered appropriate for patients with a malignancy for specified indications [5, 6]. Reasons for ICU admission in patients with cancer include postoperative care, complications caused by the malignancy and/or its treatment and crises unrelated to the tumor or its therapy [7, 8]. Amongst cancer patients the best candidates for ICU admission are those with promising treatment possibilities or when calamities occur in the absence of active malignancy [9].

Previous investigations reported on the incidence of cancer and its impact on the outcome in general ICUs [10-12]. These studies showed that a cancer diagnosis on admission to a general ICU is relatively common, varying between 13.5 to 21.5%, and that the outcome of these patients is strongly dependent on the type of admission, with planned surgical and unplanned medical admission types bearing the relatively best and worst prognosis respectively [10-12].

Although information about the influence of cancer on ICU outcome has become increasingly available during recent years [3, 4, 10-13], knowledge on the proportion and characteristics of cancer patients from a general population that is admitted to an ICU is highly limited. This information is of considerable interest, not only for insight in epidemiology and health care costs associated with different cancer diagnoses, but also for general and specialist physicians providing treatment and care to patients with a malignancy. The aim of this study was to obtain insight into which proportion of cancer patients is admitted to an ICU during the course of their illness and to analyze differences between cancer patients who were and who were not admitted to the ICU with regard to demographics, cancer diagnosis, type of treatment and outcome. Therefore, we performed a retrospective study encompassing a 5-year period and involving almost 37,000 cancer patients in the Netherlands.

Methods

Patient selection

The primary cohort consisted of all adult patients with a cancer diagnosis registered between January 1st 2006 and January 1st 2011 in four hospitals in the Netherlands. Two academic hospitals (Academic Medical Center, University of Amsterdam, Amsterdam and Leiden University Medical Center, Leiden) and two community teaching hospitals (Reinier de Graaf Hospital, Delft and Maasstad Hospital, Rotterdam) participated. Patients were selected from the hospital information systems based on encoded “Diagnosis Treatment Combinations” (DTC), a nationwide coding and reimbursement system for all patients entering a hospital, either as outpatient or inpatient, providing information about the type of care, diagnosis and all treatment modalities specified by the attending physician [14, 15]. A DTC is opened upon first contact with a patient, and the DTC starting date is registered. The choice for a DTC is made according to specific guidelines [14, 15]. For each patient a DTC remains active as long as he or she receives treatment or is in follow-up for the specified diagnosis. One patient can have more than

one DTC, for example in the presence of two different primary tumors. For the current analysis all patients with a DTC related to an oncological diagnosis were included, with the exception of patients with a primary malignancy of the central nervous system (since not all participating hospitals were primary care givers of this type of patients) or superficial skin cancer (since these tumors are not expected to lead to ICU admission or to influence survival). To identify patients from this primary cohort who were admitted to an ICU during the study period, data were linked to the database of the Dutch National Intensive Care Evaluation (NICE) registry using a deterministic linkage algorithm [16, 17]. NICE contains information on all admissions to the ICUs of 84 hospitals in the country (i.e. approximately 90% of all ICUs in the Netherlands) [18, 19]. NICE collects variables for each ICU admission including demographic data, reasons for ICU admission, comorbidities, severity of illness (APACHE IV) during the first 24 hours of ICU admission, and the ICU and in-hospital mortality and length of stay. In order to avoid patient identification, identifying variables such as hospital patient ID and the first four letters of the surname are included in an encrypted form in NICE. For the current analysis, patient identifying information in the DTC database derived from the hospital information systems were encrypted based on the same encryption algorithm as used in NICE. ICU admissions were linked with patients from the primary cohort in case the DTC encoding cancer was either active or closed less than one year before ICU admission. The date of death was extracted from the hospital information systems and the NICE registry.

Ethics

The need for ethical committee approval was waived by the Dutch Central Committee on Research Involving Human Subjects, because the study was purely observational and because only de-identified patient data were used.

Statistical analysis

Samples median test was used to test whether the median age differed for patients with and without ICU admission. Pearson chi-squared test was used to evaluate whether the distribution of the different categories of variables age, gender, phase of active cancer treatment, therapy combination and type of cancer differed between cancer patients with and without ICU admission.

General Linear Models (GLM) analyses were used to determine the contribution of the type of cancer on admission to the ICU during an active cancer diagnosis. The calculated odds ratios were adjusted for gender, phase of active cancer treatment, therapy combinations, and age. Time to ICU admission was defined as time from first day of the first DTC until ICU admission. Patients were censored at one year after the last DTC was closed (end of follow up). Furthermore, patients of whom the last DTC was not closed before January 1, 2011 and no ICU admission was found before January 1, 2012 were censored at January 1 2012. Cumulative percentages after 30 days, 365 days and 730 days of ICU admission were obtained by calculating survival tables for type of cancer and gender. The log rank (Mantel-Cox) test was performed to test whether cumulative survival differed between men and women. For all cancer diagnoses a Kaplan-Meier curve was constructed for time to ICU admission.

To analyze survival after ICU admission for patients with one or more ICU admissions during an active cancer diagnosis, Kaplan-Meier curves were plotted for different types of cancer and for gender. First ICU admission date was chosen as starting time, date of death was the endpoint.

Table 1: Study Population Demographics

	All (% ICU admission)	ICU admission (% within this group)	no ICU admission (% within this group)	p[2]
All patients	36,860 (6.4)	2,374	34,486	*<0.001*
Number of cancer diagnosis	40,716 (6.0)	2,458	38,258	*<0.001*
Age (years)				
median Interquartile range	63 (52-72)	66 (57-73)	62 (52-72)	*<0.001*
< 45 y	5,186 (2.8)	143 (6.0)	5,043 (14.6)	*<0.001*
45-65 y	11,063 (5.8)	646 (27.2)	10,417 (30.2)	*<0.001*
>60-75 y	14,323 (8.1)	1,158 (48.8)	13,165 (38.2)	*<0.001*
>75 y	6,288 (6.8)	427 (18.0)	5,861 (17.0)	*0.214*
Gender				
Male	16,967 (9.3)	1,581 (66.6)	15,386 (44.6)	*<0.001*
Female	19,893 (4.0)	793 (33.4)	19,100 (55.4)	*<0.001*
Phase of Active Cancer Treatment				
Curable solid tumors	7,770 (13.4)	1,038 (42.2)	6,732 (17.6)	*<0.001*
Incurable solid tumors	4,190 (4.6)	194 (7.9)	3,996 (10.4)	*<0.001*
Hematological malignancies	4,263 (7.1)	304 (12.4)	3,959 (10.3)	*0.002*
Follow up / maintains	24,493 (3.8)	922 (37.5)	23,571 (61.6)	*<0.001*
Treatment (combinations[1])				
Surgery	7,661 (11.8)	904 (36.8)	6,757 (17.7)	*<0.001*
Surgery and Chemotherapy	2,044 (9.3)	190 (7.7)	1,854 (4.8)	*<0.001*
Surgery and Radiation Therapy	1,289 (8.1)	104 (4.2)	1,185 (3.1)	*0.002*
Surgery, Chemotherapy, Radiation Therapy	914 (10.5)	96 (3.9)	818 (2.1)	*<0.001*
Chemotherapy	3,426 (6.2)	213 (8.7)	3,213 (8.4)	*0.137*
Chemotherapy and Radiation Therapy	1,238 (7.0)	87 (3.5)	1,151 (3.0)	*0.309*
Radiation Therapy	7,502 (2.3)	169 (6.9)	7,333 (19.2)	*<0.001*
Palliative care	911 (4.2)	38 (1.5)	873 (2.3)	*0.017*
Other/none	15,731 (4.2)	657 (26.7)	15,074 (39.4)	*<0.001*

[1] Combinations of treatments are indicated independent of the order in which these were provided.

[2] p: ICU admission versus no ICU admission.

To compare survival after the first diagnosis of cancer between patients with and without ICU admissions during an active cancer diagnosis Kaplan-Meier curves and Cox Proportional Hazard (Cox PH) regression were applied. The starting date of het first DTC was chosen as starting time, date of death was the endpoint. Patients of whom the last DTC was closed when they were still alive were censored at the day the last DTC was closed. Furthermore, patients of which the last DTC was not closed before January 1 2011, were censored at January 1 2011.

The calculated hazard ratio was adjusted for gender, phase of active cancer treatment, therapy combinations, types of cancer and age. Age was modeled using natural cubic regression splines [20], with four degrees of freedom in both Cox PH regression and logistic regression. The appropriate number of degrees of freedom was assessed by univariate analyses using analysis of variance (ANOVA). The proportional Hazard assumption was tested. For all analyses p-values below 0.05 were considered statistically significant.

Results

Patients and ICU admissions

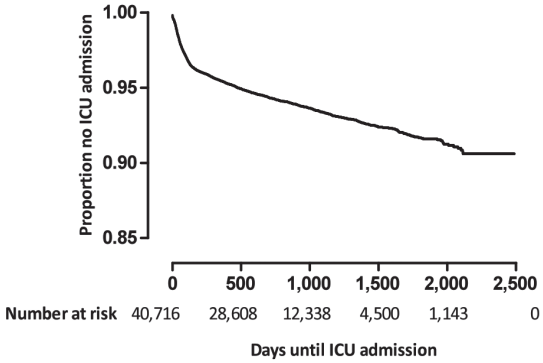
The primary cohort consisted of 36,860 patients with in total 40,716 cancer diagnoses, indicating that approximately 10% of patients had more than one cancer diagnosis (Table 1). Between January 1st 2006 and January 1st 2011 2,374 of these patients (6.4%) were admitted at least once to the ICU. Patients admitted to the ICU were older (median age 66 years) than patients not admitted to the ICU (median age 62 years, $p < 0.001$). The proportion of cancer patients admitted to the ICU was highest in the age group 60-75 years (7.6%) and lowest in the age group < 45 years (2.6%). Supplementary Table 1 shows the age distribution stratified according to cancer diagnosis. The phase and type of active cancer treatment were analyzed according ICU admission or not (Table 1), revealing that the proportion of active treatments with curative intent for a solid tumor was much greater in the ICU group (42.2%) than in the non-ICU group (17.6%, $p < 0.001$). As a comparison, the fraction of hematological malignancies in the ICU group was only modestly higher (12.4%) than in the non-ICU group (10.3%, $p < 0.002$). The proportion of incurable solid tumors and malignancies in follow-up were lower in the ICU group (both $p < 0.001$). With regard to different cancer therapies, most ICU admissions involved cancers that received surgical treatment only (11.8% of all cancers in the primary cohort and 36.8% of all ICU admissions). As a comparison, only 17.7% of cancers that did not require ICU admission received surgical therapy only. Moreover, all therapy combinations that included surgery resulted in relatively higher ICU admission rates. Supplementary Table 2 shows the distribution of different types of cancer treatment in the primary cohort and percentage ICU admission stratified according to cancer diagnosis. Figure 1 shows the time to ICU admission from opening of the DTC for all patients by Kaplan-Meier curve, revealing that most ICU admissions in cancer patients take place in the first year.

Different types of malignancy

The most frequent types of malignancy in the primary cohort were breast cancer (20.2% of all cancer diagnoses), hematological malignancy (10.5%), lung cancer (8.7%), colorectal carcinoma (8.3%), and prostate cancer (7.2%) (Table 2). Esophageal cancer most commonly lead to ICU admission (27.3% of patients with this diagnosis, Table 2); in accordance, esophageal cancer was after adjustment still associated with the highest odds ratio (3.27) for ICU admission amongst all cancer diagnoses (Table 3). Patients with other types of gastrointestinal cancer, including colorectal (10.4%) and pancreatic and biliary cancer (9.4%), lung cancer (6.3%) and patients with hematological malignancies (6.2%) also were relatively frequently admitted to the ICU (Table 2).

Figure 1: Kaplan-Meier curve for time until intensive care unit admission for all cancer diagnoses

ICU admission	
30 days	1.13 %
365 days	4.58 %
770 days	5.72 %



The graph shows the time to ICU admission from opening of the Diagnosis Treatment Combination for all 40.716 cancer diagnoses.

Indications for ICU admissions

According to the APACHE IV ICU admission diagnoses, only 26.9% of ICU admissions were directly linked with cancer (Table 4). 56.2% of ICU admissions were surgical versus 43.6% medical. 23.6% of all ICU admissions of patients were associated with surgery for cancer, whereas 32.6% of admissions were associated with surgery not directly related to the cancer diagnosis. Only 3.3% of ICU admissions were medical and directly linked with cancer; the majority of medical admissions were because of infection and sepsis (18.5% of all ICU admissions of cancer patients).

Gender differences

The primary cohort of cancer patients comprised more women (54.0%) than men (Table 1). In contrast, in the ICU group the proportion of men was much higher (66.6%, versus 44.6% men in the non-ICU group, $P < 0.001$). Compared to female patients, the proportion of male cancer patients admitted to an ICU was much higher (9.3 versus 4.0%, $P < 0.001$). This gender difference with more men than women admitted to the ICU was present in all cancer diagnosis specific subgroups, although differences for esophageal cancer and melanoma did not reach statistical significance (Table 2).

Mortality

Figure 2 shows 1500-day mortality stratified according to ICU admission status. Clearly, patients who were admitted to the ICU had a strongly reduced survival (median survival time 771 days) when compared with patients who were not admitted to the ICU (median survival time not reached during the observation period; $p < 0.001$). Figure 3 shows survival data of cancer patients admitted to the ICU stratified according gender; median survival times were 590 days for men and 497 days for women (not significant). Figure 4A-J shows survival of patients admit-

Table 2: Cumulative Intensive Care Unit Admission stratified according to cancer diagnosis and gender

	Number			30 days ICU admission (%)[2]				365 days ICU admission (%)[2]				730 days ICU admission (%)[2]			
	(%)[1]	M & F		All	M	F	*p*	All	M	F	*p*	All	M	F	*p*
Non-gender specific malignancy															
Lung cancer	3,546	(8.7)	2,125 & 1,421	1.6	2.0	1.1	*0.474*	5.3	6.2	4.0	*0.061*	6.3	7.5	4.4	*0.003*
Head and neck cancer	1,876	(4.6)	1,017 & 859	0.9	0.9	0.9	*0.676*	3.7	4.7	2.6	*0.131*	5.2	6.6	3.5	*0.001*
Colorectal cancer	3,389	(8.3)	1,817 & 1,572	2.3	2.3	2.3	*0.660*	8.4	9.9	6.7	*0.263*	10.4	11.9	8.7	*0.003*
Pancreatic, biliary cancer	2,759	(6.8)	1,418 & 1,341	2.8	3.2	2.3	*0.032*	8.2	9.9	6.3	*0.066*	9.4	11.1	7.6	*0.005*
Esophageal cancer	1,661	(4.1)	1,274 & 414	2.8	2.3	4.1	*0.765*	25.5	26.7	22.0	*0.214*	27.3	28.7	23.1	*0.102*
Other types of GI-cancer	1,323	(3.2)	803 & 520	2.5	2.6	2.3	*0.377*	10.4	11.7	8.5	*0.382*	11.8	13.7	9.0	*0.011*
Urinary tract cancer	2,367	(5.8)	1,612 & 755	0.9	1.0	0.8	*0.452*	4.6	5.1	3.4	*0.547*	5.5	6.2	4.1	*0.011*
Melanoma	491	(1.2)	225 & 266	0.2	0.4	0.0	*	0.8	1.8	0.0	*0.050*	1.5	2.5	0.7	*0.059*
Sarcomas	2,245	(5.5)	1,149 & 1,096	0.4	0.6	0.2	*0.170*	1.9	2.3	1.4	*0.017*	2.8	3.6	1.9	*0.019*
Hematological malignancy	4,275	(10.5)	2,370 & 1,905	1.6	1.9	1.3	*0.675*	4.7	5.8	3.3	*0.332*	6.2	7.7	4.4	*<0.001*
Other types of cancer	2,162	(5.3)	1,048 & 1,114	1.4	1.8	1.1	*0.293*	3.3	4.0	2.6	*0.193*	4.2	5.4	3.0	*0.201*
Gender specific malignancy															
Breast cancer	8,241	(20.2)		0.1				0.5				1.2			
Ovarian, endometrial cancer	1,598	(3.9)		0.8				1.4				1.5			
Cervical cancer	1,015	(2.5)		0.0				0.3				0.9			
Other types of gyn. cancer	446	(1.1)		0.0				0.4				0.8			
Prostate cancer	2,927	(7.2)		0.1				1.3				3.0			
Testicular cancer	395	(1.0)		0.0				1.0				1.6			

[1] % of all cancer diagnoses, [2] % of type of cancer in this cohort of 40.716 cancer diagnoses

**no comparison analysis is performed because the factor variable has only one value for every stratum. M is Male, F is Female.*

Table 3: Logistic regression for ICU admission for different types of cancer

	Odds ratio[1] (95% Confidence Interval)	*p*
Non-gender specific malignancy		
Lung cancer	Reference	
Head and neck cancer	0.96 (0.77 – 1.19)	*0.707*
Colorectal cancer	0.94 (0.79 – 1.12)	*0.468*
Pancreatic and biliary cancer	1.06 (0.88 – 1.28)	*0.527*
Esophageal cancer	3.27 (2.74 – 3.89)	*<0.001*
Other types of GI-cancer	1.18 (0.96 – 1.45)	*0.126*
Urinary tract cancer	0.48 (0.39 – 0.60)	*<0.001*
Melanoma	0.23 (0.12 – 0.43)	*<0.001*
Sarcomas	0.39 (0.29 – 0.51)	*<0.001*
Hematological malignancy	0.62 (0.08 – 5.15)	*0.661*
Other types of cancer	0.75 (0.59 – 0.95)	*0.018*
Gender specific malignancy		
Breast cancer	0.20 (0.15 – 0.25)	*<0.001*
Ovarian and endometrial cancer	0.21 (0.15 – 0.31)	*<0.001*
Cervical cancer	0.09 (0.04 – 0.18)	*<0.001*
Other types of gynecological cancer	0.10 (0.04 – 0.26)	*<0.001*
Prostate cancer	0.26 (0.21 – 0.32)	*<0.001*
Testicular cancer	0.19 (0.09 – 0.39)	*<0.001*

[1] The calculated odds ratios were adjusted for gender, phase of active cancer treatment, therapy combinations, type of cancer and age by adding these covariates in the logistic regression model.

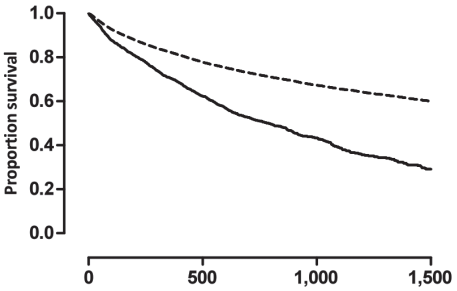
Table 4: Reason for admission in the ICU

Type of ICU admission based on APACHE IV (%)		
Surgery for cancer	579	(23.6)
Other types of surgery		
- Gastro-intestinal surgery	322	(13.1)
- Respiratory tract surgery (other than cancer)	163	(6.6)
- Cardiovascular surgery	196	(8.0)
- Other	121	(4.9)
Medical cancer	80	(3.3)
Other types of non-surgical admissions		
- Cardiac	173	(7.0)
- Respiratory	143	(5.8)
- Infection / sepsis	455	(18.5)
- Thrombosis / hemorrhage	91	(3.7)
- Neurological	44	(1.8)
Other non-surgical causes for ICU admission	87	(3.5)
Missing	4	(0.2)

Figure 2: Survival of cancer patients with or without ICU-admission

	IC admission ——	no IC admission -----
Survival		
30 days	0.96	0.98
365 days	0.70	0.82
730 days	0.51	0.72
50%*	771 days	

**p= <0.001*



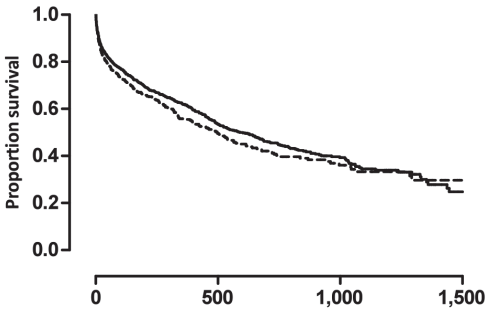
Number at risk				
IC admission	2,374	853	315	81
no IC admission	34,484	12,819	5,410	1,514

Survival of cancer patients who were (solid line) or who were not (dotted line) admitted to the ICU. This analysis encompassed 36,860 adult patients registered with a cancer diagnosis between January 1st 2006 and January 1st 2011 in four hospitals in the Netherlands. Of these patients, 2,374 were admitted to the ICU during the study period. The graph shows Kaplan-Meier curves starting at the date of cancer diagnosis registration; p value indicates the difference between groups.

Figure 3: Kaplan-Meier survival curve of cancer patients stratified by gender

	Male ——	Female -----
Survival		
30 days	0.82	0.78
365 days	0.60	0.53
730 days	0.44	0.38
50%*	590 days	497 days

**p= 0.110*



Kaplan-Meier curves starting at the date of ICU admission. Men (solid line) and women (dotted line); p value indicates the difference between groups.

ted to the ICU stratified according to cancer diagnosis. Median survival times were relatively long for prostate cancer (not reached within 4 years), breast cancer (959 days) and esophageal cancer (774 days), and relatively short for hematological malignancies (41 days).

Discussion

To the best of our knowledge our study is the first to report on the proportion of cancer patients from the general population that is admitted to an ICU during the course of their illness, stratified according to cancer diagnosis and phase and type of treatment. Of 36,860 patients registered in four hospitals with at least one cancer diagnosis 6.4% was admitted to the ICU. Of all solid tumors treated with curative intent, 13.4% were admitted to the ICU. Of all solid tumors considered incurable, still 4.6% received ICU care. Surgery was the most common treatment associated with ICU admission: of all cancers treated with surgery solely or in combination with other modalities 10.9% required ICU care. Among different cancer diagnoses, patients with esophageal cancer entered the ICU most frequently (27.3%).

Previous studies have documented that most ICU admissions of cancer patients involve postoperative care after elective surgery [17, 21, 22]. Accordingly, our data show that the majority of cancer patients entered the ICU during the course of their disease because of surgical treatment. Of interest, however, of all cancer patients who were admitted to the ICU for surgical reasons, only 41.9% of cases involved surgical treatment directly related to cancer. Hence, more than half of cases were related to surgical interventions not directly linked with the primary cancer diagnosis, most notably gastrointestinal and cardiovascular surgery. In accordance with previous investigations [12, 23-25], infection and sepsis were the most common indications for admission in medical cancer patients.

Although in this population of cancer patients women were more prevalent than men, the proportion of men that entered the ICU was more than twice as large when compared with women. While for the overall population this gender difference can be partly explained by the high prevalence of breast cancer (which very rarely results in ICU admission), men more often entered the ICU across all cancer diagnoses. Previous studies, performed in general populations (i.e., not restricted to cancer patients), also indicated that men are more likely to receive ICU care [26-29]. A large population-based study conducted in Canada demonstrated that older women with critical illness were less likely than critically ill men to be admitted to an ICU [28]. Similarly, a prospective study involving 25,998 adult patients admitted to 31 ICUs in Austria documented gender-related differences in ICU care, with male patients - despite presenting with a lower severity of illness - more likely than female patients to receive a high level of care, as defined by the number of invasive procedures [27]. Although in that investigation women had a higher observed mortality rate than men, there was no difference in outcome after adjustment for the severity of illness [27]. Overall ICU mortality did not differ between sexes in another study [30]. Our current study extends these data by showing that long-term survival of cancer patients admitted to the ICU does not differ between men and women. At present it is unclear what drives the apparent gender difference with regard to ICU admission of cancer patients, although some studies have suggested that males have more comorbid conditions at the point of cancer diagnosis, which may drive more frequent ICU admission [31-34].

According to literature, more than 60% of cancer patients have an expected survival beyond 5 years [1, 35], illustrating the need to study long-term outcome in patients with a

malignancy. Previous studies of long-term survival of ICU patients have suggested an increase in mortality during several years after hospital discharge when compared with an age- and gender-matched population [36, 37]. Among different diagnoses, cancer patients had the greatest relative risk of mortality (more than 3-fold) during 5 years after hospital discharge following ICU admission in a cohort of 12,180 ICU patients from 25 hospitals in Finland [37]. In accordance, the presence of a new malignancy was associated with a high risk of death within the first year after discharge (hazard ration 4.60) in a single-center study conducted in Australia comprising almost 20,000 ICU patients that survived to discharge [38]. A more recent study conducted in the Netherlands analyzed mortality up to 3 years after hospital discharge of patients who had received ICU care. Whereas 1- and 3-year mortalities after hospital discharge were 12.5% and 27.5% respectively for the total ICU population, in cancer patients mortality was almost twice as high at both time points [17]; these data are in line with our current long-term survival data of cancer patients after ICU admission. Although these data cannot be compared directly, they support that ICU admission involves a selection of patients with relatively favorable therapeutic perspectives, for example because major surgery requiring postoperative ICU care will be limited to patients with early stage solid tumors carrying the better prognosis. The finding that in our overall population cancer patients who were not admitted to the ICU did much better than patients who were not admitted to the ICU (Figure 2) appears to contradict this hypothesis, but may be explained by the fact that certain cancer diagnoses, such as breast and prostate cancer, have a relatively favorable prognosis and are overrepresented in the group of patients without ICU admission during follow-up (Table 2).

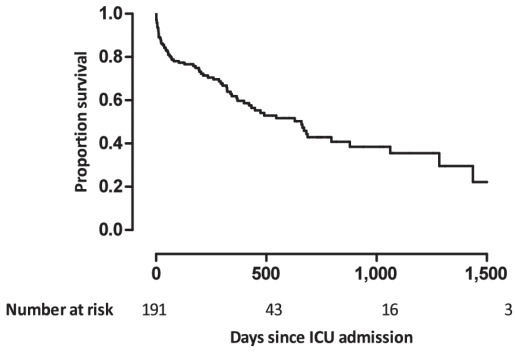
A limitation of this and previous studies that addressed long-term outcome after ICU admission [17, 36-38] is that causes of death after hospital discharge were not specified and may be unrelated to ICU admission or cancer diagnosis. In addition, since 90% of all ICUs participate in the NICE registry we may have missed ICU referrals of some patients enrolled in our general cohort.

In conclusion, we report detailed information about the subgroup of cancer patients admitted to an ICU during a 5-year study period, comparing their demographics, diagnoses, phase and type of therapy with those in patients from the same cohort who did not receive ICU care. Patients with gastrointestinal malignancies, most notably esophageal cancer, were most often admitted to the ICU. In accordance, most patients entered the ICU for postoperative care. Our long-term survival analysis of patients who received ICU care shows that the use of aggressive support measures for cancer patients is not futile.

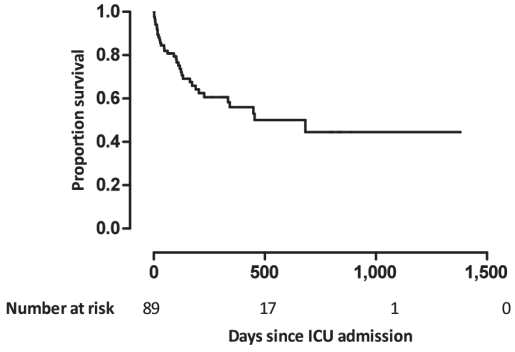
Figure 4: Kaplan Meijer survival curve of cancer patients according to type of cancer (A-J)

(A) Lung cancer, (B) Head and neck cancer, (C) Colorectal cancer, (D) Pancreatic and biliary cancer, (E) Esophageal cancer, (F) Other types of gastrointestinal cancer, (G) Urinary tract cancer, (H) Hematological malignancy, (I) Breast cancer, (J) Prostate cancer

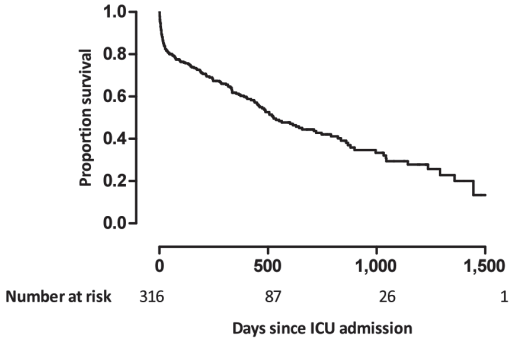
A. Lung cancer	
Survival	
30 days	0.82
365 days	0.60
730 days	0.41
50%	659 days



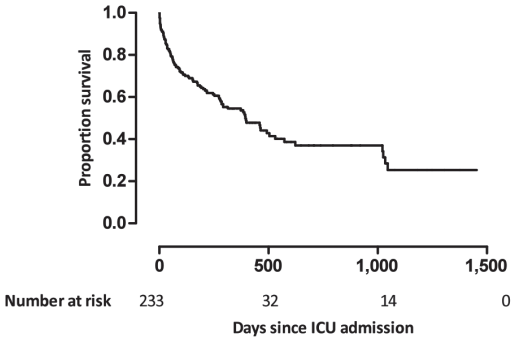
B. Head and neck cancer	
Survival	
30 days	0.83
365 days	0.54
730 days	0.43
50%	683 days



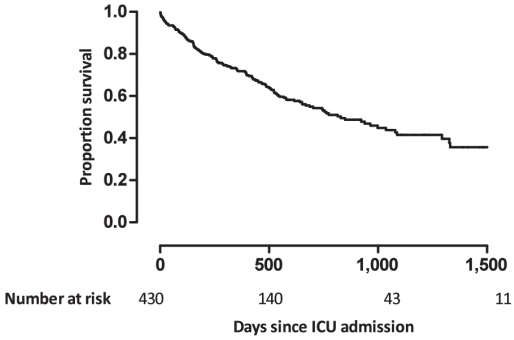
C. Colorectal cancer	
Survival	
30 days	0.79
365 days	0.59
730 days	0.41
50%	526 days



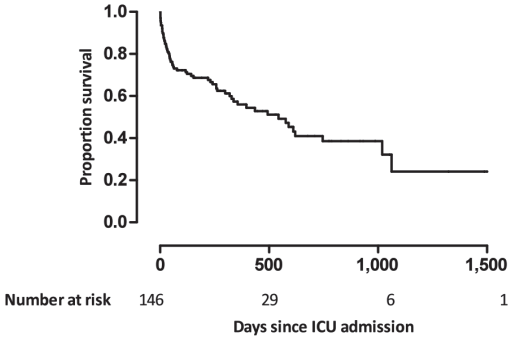
D. Pancreatic and biliary cancer	
Survival	
30 days	0.82
365 days	0.52
730 days	0.36
50%	394 days



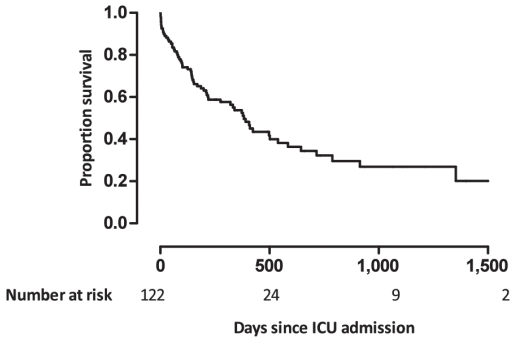
E. Esophageal cancer	
Survival	
30 days	0.93
365 days	0.71
730 days	0.54
50%	829 days



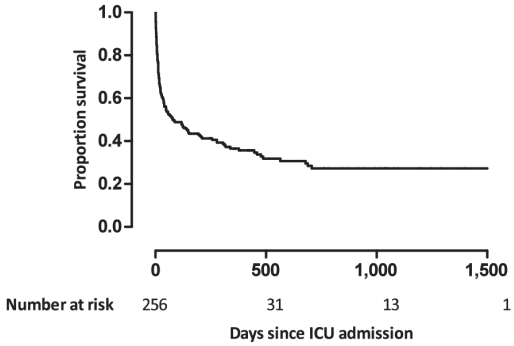
F. Other types of GI-cancer	
Survival	
30 days	0.79
365 days	0.54
730 days	0.39
50%	543 days



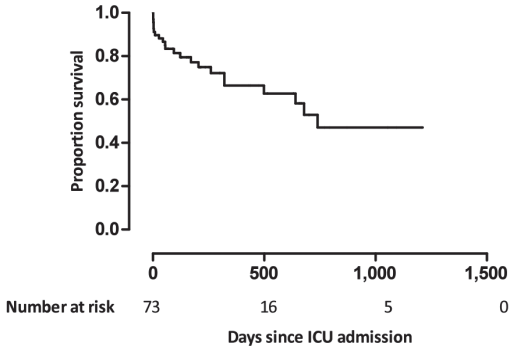
G. Urinary tract cancer	
Survival	
30 days	0.87
365 days	0.53
730 days	0.32
50%	383 days



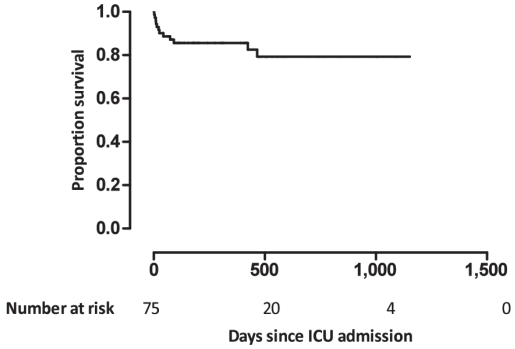
H. Hematological malignancy	
Survival	
30 days	0.54
365 days	0.33
730 days	0.24
50%	78 days



I. Breast cancer	
Survival	
30 days	0.82
365 days	0.62
730 days	0.49
50%	679 days



J. Prostate cancer	
Survival	
30 days	0.88
365 days	0.83
730 days	0.77



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Supplementary Table 1: Cumulative Intensive Care Unit Admission for the Different Age Groups

	< 45 years			45-60 years			60-75 years			>75 years		
	All	ICU (%)		All	ICU (%)		All	ICU (%)		All	ICU (%)	
Non-gender specific malignancy												
Lung cancer	114	7	(6.1)	990	70	(7.1)	1,649	119	(7.2)	793	26	(3.3)
Head and neck cancer	335	10	(3.0)	617	32	(5.2)	672	61	(9.1)	252	16	(6.3)
Colorectal cancer	169	4	(2.4)	809	61	(7.5)	1,467	155	(10.6)	944	134	(14.2)
Pancreatic and biliary cancer	190	5	(2.6)	833	66	(7.9)	1,248	139	(11.1)	488	42	(8.6)
Esophageal cancer	43	12	(27.9)	503	145	(28.8)	795	239	(30.1)	320	54	(16.9)
Other types of GI-cancer	136	8	(5.9)	394	46	(11.7)	568	68	(12.0)	225	35	(15.6)
Urinary tract cancer	219	7	(3.2)	580	31	(5.3)	954	74	(7.8)	614	38	(6.2)
Melanoma	131	2	(1.5)	176	3	(1.7)	132	5	(3.8)	62	10	(16.1)
Sarcomas	826	18	(2.2)	575	16	(2.8)	549	20	(3.6)	285	0	(0.0)
Hematological malignancy	990	45	(4.5)	1,261	111	(8.8)	1,336	117	(8.8)	688	32	(4.7)
Other types of cancer	723	14	(1.9)	465	20	(4.3)	580	42	(7.2)	394	7	(1.8)
Gender specific malignancy												
Breast cancer	854	9	(1.1)	3402	40	(1.2)	3,032	50	(1.6)	953	23	(2.4)
Ovarian and endometrial cancer	162	0	(0.0)	528	9	(1.7)	661	12	(1.8)	247	12	(4.9)
Cervical cancer	464	1	(0.2)	341	2	(0.6)	137	5	(3.6)	73	0	(0.0)
Other types of gynecological cancer	51	2	(3.9)	108	0	(0.0)	129	2	(1.6)	158	0	(0.0)
Prostate cancer	7	0	(0.0)	485	10	(2.1)	1,881	85	(4.5)	554	23	(4.2)
Testicular cancer	283	4	(1.4)	91	1	(1.1)	14	2	(14.3)	7	0	(0.0)
Total	**5,697**	**148**	**(2.6)**	**12,158**	**663**	**(5.5)**	**15,804**	**1,195**	**(7.6)**	**7,057**	**452**	**(6.4)**

Supplementary Table 2: Cumulative Intensive Care Unit admissions according to cancer diagnosis and type of treatment

	Surgery			Surgery and Chemotherapy			Surgery and Radiation Therapy			Surgery, Chemo-therapy and Radiation Therapy		
Non-gender specific malignancy	**All**	**ICU**	**(%)**	**All**	**ICU**	**(%)**	**All**	**ICU**	**(%)**	**All**	**ICU**	**(%)**
Lung cancer	221	98	(44.3)	57	12	(21.1)	27	2	(7.4)	33	3	(9.1)
Head and neck cancer	246	27	(11.0)	32	0	(0.0)	112	24	(21.4)	40	7	(17.5)
Colorectal cancer	1,126	243	(21.6)	389	30	(7.7)	141	41	(29.1)	89	9	(10.1)
Pancreatic, biliary cancer	718	200	(27.9)	119	3	(2.5)	21	4	(19.0)	7	0	(0.0)
Esophageal cancer	347	247	(71.2)	179	102	(57.0)	44	31	(70.5)	132	79	(59.8)
Other types of GI-cancer	442	123	(27.8)	96	22	(22.9)	10	1	(10.0)	19	3	(15.8)
Urinary tract cancer	1,053	102	(9.7)	323	23	(7.1)	40	10	(25.0)	40	6	(15.0)
Melanoma	132	4	(3.0)	61	0	(0.0)	79	0	(0.0)	7	1	(14.3)
Sarcomas	463	18	(3.9)	25	13	(52.0)	89	10	(11.2)	29	2	(6.9)
Hematological malignancy	13	3	(23.1)	8	8	(0.0)	0	0	(0.0)	15	4	(26.7)
Other types of cancer	477	49	(10.3)	520	2	(0.4)	31	1	(3.2)	3	0	(0.0)
Gender specific malignancy												
Breast cancer	587	11	(1.9)	526	8	(1.5)	317	5	(1.6)	472	6	(1.3)
Ovarian, endometrial cancer	744	18	(2.4)	142	6	(4.2)	76	1	(1.3)	8	0	(0.0)
Cervical cancer	354	1	(0.3)	11	0	(0.0)	143	1	(0.7)	33	0	(0.0)
Other types of gyn. cancer	201	2	(1.0)	0	0	(0.0)	37	0	(0.0)	0	0	(0.0)
Prostate cancer	758	40	(5.3)	20	2	(10.0)	216	9	(4.2)	7	1	(14.3)
Testicular cancer	64	3	(4.7)	30	1	(3.3)	12	0	(0.0)	5	0	(0.0)
Total	**7,946**	**1,189**	**(15.0)**	**2,538**	**232**	**(9.1)**	**1395**	**140**	**(10.0)**	**939**	**121**	**(12.9)**

Continuing Supplementary Table 2

Chemotherapy and Radiation Therapy			Chemotherapy			Radiation therapy			Palliative Care			Other, none		
All	**ICU**	**(%)**	**All**	**ICU**	**(%)**	**All**	**ICU**	**(%)**	**All**	**ICU**	**(%)**	**All**	**ICU**	**(%)**
372	13	(3.5)	527	17	(3.2)	1,256	34	(2.7)	35	0	(0.0)	1,065	90	(8.5)
52	4	(7.7)	64	4	(6.3)	547	13	(2.4)	12	0	(0.0)	800	69	(8.6)
92	12	(13.0)	210	4	(1.9)	71	17	(23.9)	83	3	(3.6)	1,292	99	(7.7)
30	0	(0.0)	193	2	(1.0)	17	3	(17.6)	108	2	(1.9)	1,629	121	(7.4)
112	13	(11.6)	147	19	(12.9)	82	5	(6.1)	45	3	(6.7)	712	90	(12.6)
14	2	(14.3)	94	3	(3.2)	12	1	(8.3)	69	3	(4.3)	620	52	(8.4)
35	2	(5.7)	178	13	(7.3)	38	3	(7.9)	38	4	(10.5)	668	33	(4.9)
17	2	(11.8)	29	0	(0.0)	11	0	(0.9)	13	0	(0.0)	288	4	(1.4)
30	0	(0.0)	97	7	(7.2)	513	10	(1.8)	11	0	(0.0)	949	15	(1.6)
202	48	(23.8)	1,433	207	(14.4)	70	9	(15.7)	272	24	(8.8)	2,312	111	(4.8)
16	0	(0.0)	71	5	(7.0)	298	11	(3.7)	152	3	(2.0)	1,131	43	(3.8)
224	5	(2.2)	292	3	(1.0)	3,955	65	(1.6)	36	0	(0.0)	1,840	27	(1.5)
9	0	(0.0)	28	4	(14.3)	85	4	(4.7)	11	0	(0.0)	501	6	(1.2)
13	0	(0.0)	7	0	(0.0)	84	1	(1.2)	7	1	(14.3)	363	4	(1.1)
0	0	(0.0)	58	0	(0.0)	10	0	(0.0)	0	0	(0.0)	199	3	(1.5)
23	1	(43)	74	1	(1.4)	494	28	(5.7)	24	1	(4.2)	1,340	58	(4.3)
13	1	(7.7)	75	2	(2.7)	5	0	(0.0)	1	0	(0.0)	191	1	(0.5)
1,254	**103**	**(8.2)**	**3,577**	**291**	**(8.1)**	**7,548**	**204**	**(2.7)**	**917**	**44**	**(4.8)**	**15,900**	**826**	**(5.2)**

OUTCOMES OF CANCER PATIENTS AFTER UNPLANNED ADMISSION TO GENERAL INTENSIVE CARE UNITS

CHAPTER 3

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Abstract

Background: Acute admission to an intensive care unit (ICU) of cancer patients is considered with increasing frequency due to a better life expectancy and more aggressive therapies. The aim of this study was to determine the characteristics and outcomes of cancer patients with unplanned admissions to general ICUs, and to compare these with outcomes of critically ill patients without cancer.
Materials and Methods: All unplanned ICU admissions in the Netherlands collected in the National Intensive Care Evaluation registry between January 2007 and January 2011 were analyzed.
Results and Conclusion: Of the 140,154 patients with unplanned ICU admission 10.9 % had a malignancy. Medical cancer patients were more severely ill on ICU admission in comparison with medical non-cancer patients, as reflected by higher needs for mechanical ventilation (50.8% vs 46.4%, $p<0.001$) and vasopressors within 24 hours after admission (41.5% vs 33.0%, $p<0.001$), higher Acute Physiology and Chronic Health Evaluation (APACHE) IV scores (88.1 vs 67.5, $p<0.001$) and a longer ICU stay (5.1 vs 4.6 days, $p<0.001$). In contrast, surgical cancer patients only displayed a modestly higher APACHE IV score on admission when compared with non-cancer surgical patients, whereas the other afore mentioned parameters were lower in the surgical cancer patients group. In-hospital mortality was almost twice as high in medical cancer patients (40.6%) as in medical patients without cancer (23.7%). In-hospital mortality of surgical cancer patients (17.4%) was slightly higher than in patients without cancer (14.6%). These data indicate that unplanned ICU admission is associated with a high mortality in patients with cancer when admitted for medical reasons.

Introduction

Survival of cancer patients has increased over the last three decades due to a greater awareness of early signs and better treatment possibilities [1]. These treatments are more intense and may cause significant toxicity and side effects due to chemotherapy, radiation therapy and/or extensive radical surgery. The more aggressive care has led to an increase in the need for vital life support and life-sustaining treatments. Consequently, referral to an intensive care unit (ICU) is increasingly considered in cancer patients [2].

Decisions for ICU admissions in patients with advanced cancer are complex, and the knowledge of survival rates and prognostic factors is essential to these decisions. Ten years ago, in guidelines for ICU admission, a taskforce of the American College of Critical Care Medicine concluded that patients with hematological or metastasized solid malignancies are poor candidates for ICU admission considering their high risk of mortality [3]. In accordance, cancer patients are more likely to be denied ICU admission [4]. More recent data suggest that the prognosis of critically ill cancer patients admitted to an ICU has improved considerably [5, 6]. However, these encouraging data are almost exclusively derived from single-center studies conducted in specialized hemato-oncologic ICUs, which may not reflect outcome of cancer patients on general ICUs.

Two relatively large multicenter studies examined the impact of cancer on the outcome of patients admitted to general ICUs [7, 8]. These studies did not distinguish between planned and unplanned cancer patients. Many ICU admissions in cancer patients are planned, especially in the context of postoperative care. The dilemma whether or not to admit a patient with a malignancy to the ICU in particular applies to unplanned emergency situations. Therefore, the objective for the present study was to analyze the characteristics and outcome of cancer patients with unplanned admissions to general ICUs, and to compare these with outcomes of critically ill patients without cancer. For this we analyzed all ICU admissions in the Netherlands collected in the National Intensive Care Evaluation (NICE) registry from January 2007 through January 2011 [9].

Materials and Methods

Patient data

The database of the Dutch National Intensive Care Evaluation (NICE) registry was used in this observational study [9]. In 1996 the NICE foundation started collecting data on patients admitted to Dutch ICUs. The participating ICUs provide information on all ICU admissions with the aim to assess and compare the performance of the ICUs and to improve the quality of care. For each ICU admission variables are collected that describe patient characteristics, severity of illness 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, including name and patient identification number, are untraceable. 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 [10]. Data for the current study were collected from all consecutive admissions to 80 ICUs between January 2007 and January 2011. The study was strictly observational and every clinical decision was at the discretion of the responsible physician.

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 retrospective and because only anonymous patient data were used.

Selection of patients with a malignancy

Patients were identified as being admitted with a malignancy when their APACHE IV reason for admission contained the term cancer, neoplasm, leukemia, lymphoma, malignancy and/or tumor or if one of the APACHE II fields *metastasized neoplasm* or *hematological malignancy* was chosen as co-morbid condition within the six months prior to ICU admission.

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). We used χ^2 tests for comparisons of categorical variables, independent *t* test to assess differences for normally distributed continuous variables, and the Mann-Whitney U-test to assess differences for non-normally distributed continuous variables. 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. Multivariate logistic regression analyses were performed to assess the associations between the type of malignancy and in-hospital mortality. To adjust for severity of illness, the APACHE III severity of illness score (consisted of the APACHE III/IV acute physiology score (APS), age, and comorbidities) was included in the model as covariate [10, 11]. We applied the APACHE IV inclusion criteria to select patient data for the multivariate logistic regression analyses and the calculation of SMRs [10]. Results were considered statistically significant if p-values were below 0.05. All statistical analyses were performed using PASW statistics 18 (SPSS, Chicago).

Results

Patients

251,748 patients were admitted to the participating ICUs during the study period (Figure 1). Of these, 34,067 (13.5%) had a diagnosis of malignancy on admission to the ICU; 217,681 patients (86.5%) did not have such a diagnosis. In this overall cohort, most ICU admissions in patients with a malignancy were planned (54.2% versus 45.8% unplanned); for patients without cancer most ICU admissions were unplanned (68.0% versus 32.0% planned). This difference was mainly caused by a large proportion of planned surgical procedures in cancer patients who most commonly had a very brief and uncomplicated stay on the ICU (data not shown). Since our primary objective was to examine the impact of cancer on the outcome of non-elective ICU admissions, our analysis focused on this subgroup. For this analysis 15,211 unplanned patients with a malignancy and 124,943 unplanned patients without a malignancy were available (Figure 1 and Table 1). Most unplanned ICU admissions amongst patients with cancer were for a surgical indication (59.3%), whereas most unplanned ICU admissions in non-cancer patients were for a medical reason (67.0%). Of the 15,211 unplanned patients with a malignancy, 14,087 satisfied the APACHE IV inclusion criteria and were included in the multivariate logistic regression analyses and for the calculation of SMRs.

Figure 1: Overview and selection of patients admitted to the participating ICUs from January 2007 until January 2011

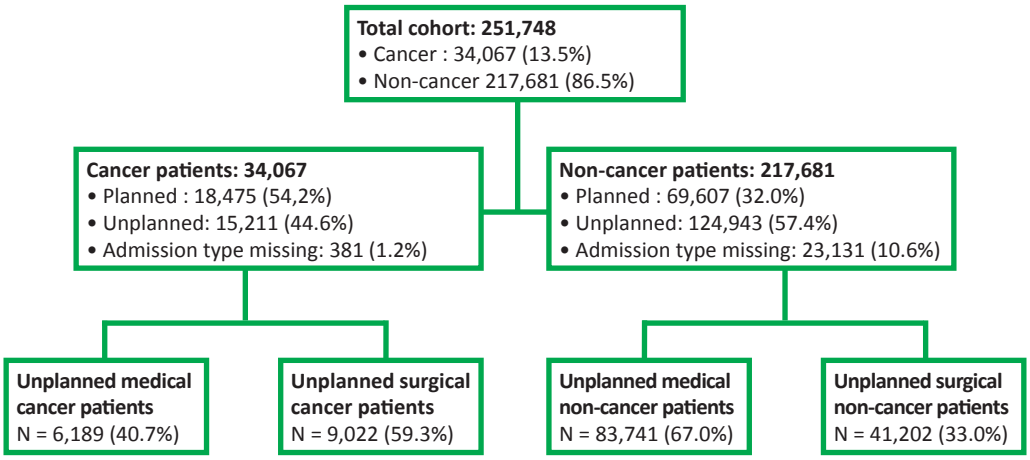


Table 1 shows patient characteristics, comorbidities and severity of illness scores of all patients with unplanned ICU admissions, stratified according to the presence or absence of cancer and the indication for admission (medical versus surgical). Medical cancer patients had a higher incidence of confirmed infection, pneumonia and sepsis when compared with medical patients without cancer. Infections (including pneumonia and sepsis) were less common in surgical patients in general and differences (albeit statistically significant) between cancer and non-cancer patients were modest at best. As expected, immunodeficiency was far more common amongst the medical cancer patients. In addition, the proportion of medical cancer patients with acute renal failure and need for vasopressors and mechanical ventilation was higher than in medical patients without a malignancy. With regard to chronic comorbidity differences between cancer and non-cancer patients were modest, with the former group harboring fewer patients with heart failure. In accordance with the observed differences in acute comorbidity, cancer patients had much higher APACHE IV scores than patients without cancer, especially those with a medical indication for ICU admission. Medical, but not surgical, cancer patients had a longer length of stay on the ICU than the corresponding patients without cancer.

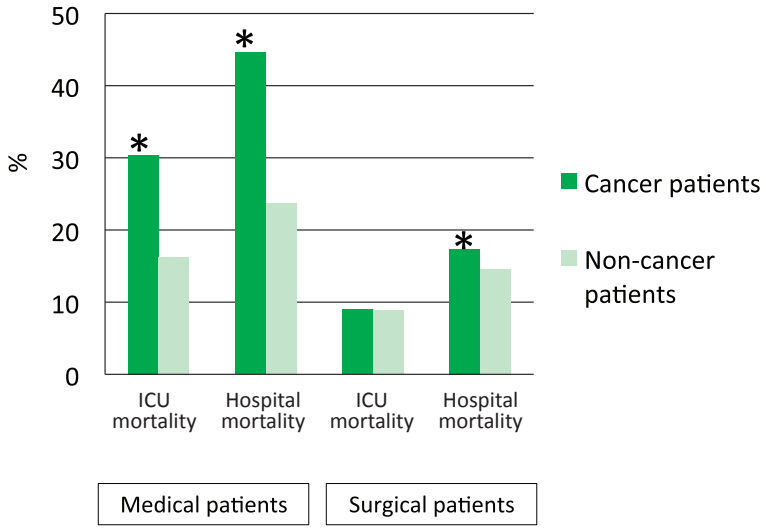
Mortality

Figure 2 shows mortality rates stratified according to distinct patient subgroups. ICU and in-hospital mortality were almost twice as high in unplanned medical cancer patients as in medical patients without cancer (ICU mortality 30.4% vs. 16.2% respectively; in-hospital mortality 44.6% vs. 23.7% respectively; both $p < 0.001$). In contrast, ICU mortality in unplanned surgical cancer patients and unplanned surgical non-cancer patients was similar (9.0% vs. 8.9% respectively; $p = 0.8$); in-hospital mortality was higher in surgical cancer patients than in surgical non-cancer patients (17.4% vs. 14.6% respectively; $p < 0.001$).

Table 1: Patient characteristics, comorbidities and severity of illness scores of all patients with unplanned ICU admissions, stratified according to indication for admission (medical versus surgical) and the presence or absence of cancer

	Unplanned Cancer patients n = 15,211			Unplanned Patients without cancer n = 124,943			Medical cancer versus medical non-cancer	Surgical cancer versus surgical non-cancer
	Medical n = 6,189	Surgical n = 9,022	*p*	Medical n = 83,741	Surgical n = 41,202	*p*	*p*	*p*
male (%)	59.5	56.8	*0.001*	56.3	55.4	*<0.001*	*<0.001*	*0.016*
age (median (IQR))	66 (58-74)	71 (61-77)	*<0.001*	64 (50-75)	67 (53-77)	*<0.001*	*<0.001*	*<0.001*
acute comorbid diseases (%)								
- confirmed infection	29.9	15.6	*<0.001*	19.9	16.5	*<0.001*	*<0.001*	*0.023*
- pneumonia	18.9	1.5	*<0.001*	16.3	0.9	*<0.001*	*<0.001*	*<0.001*
- sepsis	21.2	6.8	*<0.001*	13.2	7.4	*<0.001*	*<0.001*	*0.034*
- immunodeficiency	32.5	8.3	*<0.001*	5.7	3.5	*<0.001*	*<0.001*	*<0.001*
- cardiac dysrhythmia	10.9	5.6	*<0.001*	11.1	6.1	*<0.001*	*0.556*	*0.100*
- acute renal failure	17.5	5.6	*<0.001*	11.0	6.7	*<0.001*	*<0.001*	*<0.001*
- mechanical ventilation	50.8	40.4	*<0.001*	46.4	50.2	*<0.001*	*<0.001*	*<0.001*
- vasopressors	41.5	31.8	*<0.001*	33.0	34.7	*<0.001*	*<0.001*	*<0.001*
chronic comorbid disease (%)								
- COPD	10.9	10.1	*0.069*	15.0	9.3	*<0.001*	*<0.001*	*0.010*
- chronic renal insufficiency	6.9	3.4	*<0.001*	6.9	4.5	*<0.001*	*0.918*	*<0.001*
- heart failure	3.5	3.4	*0.788*	5.4	5.9	*0.230*	*<0.001*	*0.001*
- diabetes	12.7	11.6	*0.023*	4.5	11.9	*<0.001*	*<0.001*	*0.463*
ICU severity of illness								
- APACHE IV score (mean (SD))	88.1 (36.3)	58.4 (28.3)	*<0.001*	67.5 (36.7)	54.9 (30.4)	*<0.001*	*<0.001*	*<0.001*
- ICU length of stay (days) (median (IQR))	2.0 (0.81-5.4)	1.0 (0.79-2.9)	*<0.001*	1.8 (0.74-4.6)	1.1 (0.72-3.7)	*<0.001*	*<0.001*	*<0.001*

Figure 2: ICU and hospital mortality rates in unplanned cancer versus non-cancer population for medical and surgical patient groups



** P < 0.001 versus non-cancer patients*

Severity of illness and outcome in cancer patients

The NICE registry collects information about the primary cancer diagnosis only when cancer is one of the main reason for admission to the ICU; in other cases malignancy is scored as hematological malignancy or neoplasm/metastasized carcinoma without further specification. Table 2 shows diagnoses of cancer patients with unplanned ICU admissions. For the majority of medical cancer patients malignancy was not the main reason for ICU admission (71.8%). In medical patients for whom cancer was the primary reason for admission, the most common diagnoses included respiratory tract carcinoma (7.5%) and hematological malignancy (leukemia 5.6%; lymphoma 4.9%); in this subgroup of medical cancer patients confirmed infection was frequently present in especially patients with hematological malignancy and lower gastrointestinal carcinoma (32.4 – 40.5%)(Table 3). Mortality was high across all diagnoses, especially so in patients with hematological malignancy and respiratory tract carcinoma (hospital mortality 48.5 – 53.2%). In general, the APACHE IV model adequately predicted mortality in medical cancer patients with cancer as main reason for ICU admission, as reflected by SMRs approaching 1.00. In contrast to medical cancer patients, the majority of surgical cancer patients had cancer as main indication for ICU admission (75.8%), the most common being lower gastrointestinal carcinoma (32.2%)(Table 3). Patients with lower gastrointestinal carcinoma displayed ICU and in-hospital mortalities of 7.6% and 16.2% respectively; ICU and in-hospital mortalities amongst surgical patients with upper gastrointestinal carcinoma were also relatively high (8.2% and 15.7% respectively)(Table 4). Mortality rates amongst surgical patients with other cancer diagnoses were much lower. Notably, mortality was lower than predicted by the APACHE IV model in most subgroups of surgical cancer patients.

Table 2: Cancer diagnosis in the unplanned population in the NICE registry

All unplanned cancer patients (type of cancer) n = 15,211			
	Medical n = 6,189	Surgical n = 9,022	p
Primairy cancer diagnosis [1] (%)			
• Respiratory tract cancer	7.5	11.3	<0.001
• Leukemia	5.6	0.1	<0.001
• Lymphoma	4.9	0.2	<0.001
• Upper gastrointestinal cancer	3.9	12.3	<0.001
• CNS malignancy	2.7	5.4	<0.001
• Lower gastrointestinal cancer	2.2	32.2	<0.001
• Urological tract cancer	1.0	10.2	<0.001
• Other	0.2	1.5	<0.001
• Female cancer	0.1	2.5	<0.001
Underlying malignancy [2] (%)	**71.8**	**24.2**	**<0.001**
• Hematological malignancy	29.6	4.3	<0.001
• Metastasized solid tumor	42.2	19.8	<0.001
Total (%)	100	100	

[1] Patients admitted for a primary cancer diagnosis (APACHE IV).

[2] Patients admitted for other reasons, but having an underlying malignancy

Adjusted effect estimates of type of malignancy on in-hospital mortality

We performed multivariate logistic regression analyses to assess the associations between the type of malignancy and in-hospital mortality (Table 5). In unplanned medical cancer patients admission for respiratory tract cancer (adjusted odds ratio 2.15), upper gastrointestinal cancer (1.42) and leukemia (1.35) were associated with a higher risk for mortality. Patients with hematological cancer as comorbidity had lower risk for mortality. In unplanned surgical cancer patients adjusted risk was lower for patients admitted with respiratory tract cancer, urological cancer and female cancer whereas mortality risk was higher in patients with metastasized solid tumor as comorbidity.

Discussion

We here report on the characteristics and outcome of more than 15,000 cancer patients with an unplanned emergency admission to general ICUs. Our main finding is that medical cancer patients have strongly increased hospital mortality (40.6%) when compared with medical non-cancer patients (23.7%), which is associated with a higher incidence of acute comorbidity and a greater severity of illness on admission in the former group.

The current study used data extracted from the Dutch National Intensive Care Evaluation (NICE) database, collected during a four year period, to obtain insight in the epidemiology and outcome of cancer patients on general ICUs. Our study differs from several previous investigations that reported on prognostic factors for cancer patients on ICUs in that these mainly

Table 3: Demographic characteristics and outcomes for medical cancer patients stratified according to the type of malignancy

Unplanned medical cancer patients[1]											
Type of cancer	**Respiratory tract**	**Leukemia**	**Lymphoma**	**Upper GI**	**CNS**	**Lower GI**	**Urinary tract**	**Other**	**Female**	**Underlying malignancy**	
										Hematological	**Metastasized solid tumor**
Confirmed infection (%)	20.5	40.5	34.2	21.1	10.8	32.4	28.6	13.3	20.0	35.3	28.0
Vasopressors (%)	33.5	46.3	47.8	37.6	21.7	36.7	38.1	26.7	40.0	45.5	40.8
Mechanical ventilation (%)	60.3	62.4	55.5	39.3	57.2	36.7	39.7	26.7	20.0	56.4	44.9
Length of ICU stay (days) (median (IQR))	1.81 (0.78-3.97)	2.86 (0.85-7.50)	2.99 (0.97-7.78)	1.72 (0.77-3.79)	1.08 (0.70-2.80)	1.88 (0.82-5.00)	1.89 (0.83-4.50)	1.89 (0.90-4.75)	0.89 (0.45-1.60)	2.67 (0.98-7.33)	1.75 (0.71-4.20)
ICU mortality (%)	33.5	42.8	37.2	31.8	16.9	21.6	20.6	6.7	-	31.8	28.
Hospital mortality (%)	48.6	53.2	48.5	45.0	27.7	40.3	36.5	13.3	-	46.5	42.7
APACHE IV score (mean(SD))	77.7 (31.0)	90.6 (31.7)	94.8 (38.0)	85.1 (38.3)	66.6 (30.2)	81.6 (36.0)	78.6 (30.0)	52.2 (20.3)	69.5 (13.9)	96.3 (34.8)	87.4 (35.3)
APACHE IV SMR (CI)*	0.86 (0.74-0.98)	1.07 (0.90-1.25)	0.90 (0.74-1.07)	0.94 (0.74-1.16)	0.88 (0.63-1.17)	0.86 (0.62-1.14)	1.02 (0.60-1.54)	-	-	0.87 (0.81-0.95)	0.85 (0.79-0.91)

[1] *All patients satisfying the APACHE IV inclusion criteria.*

** Confidence Interval*

Table 4: Demographic characteristics and outcomes for surgical cancer patients stratified according to the type of malignancy

Unplanned surgical cancer patients[1]											
Type of cancer	**Respiratory tract**	**Leukemia**	**Lymphoma**	**Upper GI**	**CNS**	**Lower GI**	**Urinary tract**	**Other**	**Female**	**Underlying malignancy**	
										Hematological	**Metastasized solid tumor**
Confirmed infection (%)	4.9	20.0	40.0	11.5	2.1	13.1	6.0	5.9	6.2	28.1	35.7
Vasopressors (%)	15.3	40.0	55.0	30.8	11.1	33.8	25.9	27.9	28.6	44.5	44.9
Mechanical ventilation (%)	25.4	60.0	70.0	36.6	36.3	36.3	28.4	27.2	33.5	65.5	61.4
Length of ICU stay (days) (median (IQR))	0.91 (0.79-1.08)	0.89 (0.78-1.66)	1.83 (0.90-12.34)	1.00 (0.84-2.71)	0.85 (0.75-0.94)	0.94 (0.80-1.91)	0.90 (0.79-1.09)	0.91 (0.79-1.05)	0.88 (0.75-1.15)	1.07 (0.81-3.58)	1.12 (0.79-3.25)
ICU mortality (%)	3.2	-	25.0	8.2	4.7	7.6	3.3	2.9	3.1	17.1	18.4
Hospital mortality (%)	6.5	-	35.0	15.7	7.6	16.2	8.1	6.6	4.4	34.0	33.0
APACHE IV score (mean(SD))	43.0 (16.1)	63.0 (25.7)	83.0 (26.1)	53.5 (25.2)	37.5 (23.8)	58.7 (24.8)	50.8 (22.0)	46.8 (21.7)	51.6 (21.2)	78.1 (30.4)	74.1 (29.0)
APACHE IV SMR (CI)*	0.64 (046-0.86)	-	1.15 (0.41-2.25)	0.82 (0.68-0.96)	0.87 (0.59-1.22)	0.73 (0.66-0.81)	1.30 (0.99-1.65)	0.63 (0.25-1.18)	0.44 (0.17-0.83)	0.99 (0.80-1.20)	0.90 (0.81-0.99)

[1] *All patients satisfying the APACHE IV inclusion criteria.*

** Confidence Interval*

Table 5: Adjusted effect estimates of type of malignancy on in-hospital mortality for unplanned medical and surgical cancer patients

Adjusted Odds ratio for unplanned cancer patients (95% Confidence Interval) [1]		
	Medical (n=5,430) [2]	Surgical (n=8,657) [2]
Primary cancer diagnosis[3]		
• Respiratory tract cancer	2.15 (1.75-2.64)	0.61 (0.45-0.82)
• Leukemia	1.35 (1.06-1.71)	0.41 (0.05-3.6)
• Lymphoma	0.89 (0.68-1.18)	1.29 (0.41-4.05)
• Upper gastrointestinal cancer	1.42 (1.05-1.92)	1.05 (0.854-1.30)
• CNS malignancy	0.78 (0.54-1.12)	0.70 (0.46-1.06)
• Lower gastrointestinal cancer	0.84 (0.60-1.19)	0.97 (0.85-1.12)
• Urological tract cancer	0.83 (0.49-1.42)	0.50 (0.37-0.67)
• Female cancer	-	0.28 (0.14-0.56)
• Other	0.88 (0.18-4.34)	0.42 (0.18-0.95)
Underlying malignancy[4]		
• Hematological malignancy	0.78 (0.68-0.90)	1.30 (0.98-1.72)
• Metastasized solid tumor	0.91 (0.80-1.03)	1.77 (1.51-2.06)

[1] Adjusted for APACHE III severity of illness score.

[2] All patients satisfying the APACHE IV inclusion criteria.

[3] Patients admitted for a primary cancer diagnosis (APACHE IV).

[4] Patients admitted for other reasons, but having an underlying malignancy.

involved specialized oncologic ICUs, making extrapolation to general ICUs cumbersome [5, 6, 12]. Our investigation should be compared with two recent multicenter studies investigating the outcome of cancer patients in general ICUs [7, 8]. Taccone et al. used data collected during the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, performed during two weeks in 198 ICUs from 24 European countries, to assess the characteristics and outcome of 473 cancer patients in general ICUs [7]. Soares et al. prospectively enrolled 717 cancer patients in a two-month observational study performed in 28 Brazilian ICUs [8]. Important differences between these studies and ours include the number of patients evaluated (140,154 of whom 15,211 with a cancer diagnosis in the current investigation) and the period during which data were collected (four years). In addition, our study focused on unplanned emergency ICU admissions, considering that this type of admission represents a common dilemma for clinicians. Whereas Taccone et al. [7] did not discriminate between planned and unplanned admissions, Soares and colleagues [8] distinguished medical patients versus scheduled and emergency surgical patients. These two previous investigations together with the present study indicate that a cancer diagnosis on admission to a general ICU is far from seldom: in our overall cohort (comprising 251,748 patients), 13.5% of patients admitted to the ICU had a diagnosis of malignancy versus 15.0% in the SOAP cohort [7] and 21.5% in the Brazilian study [8]. The current investigation further shows that amongst unplanned ICU admissions the proportion of cancer patients is lower (15,211 of 140,154 or 10.9%), which may reflect the reduced willingness of clinicians to admit cancer patients to the ICU in emergency situations.

Mortality rates especially differed between medical cancer and non-cancer patients, whereas differences between surgical cancer and non-cancer patients were either not existing (ICU mortality: 9.0 versus 8.9% respectively) or modest (hospital mortality: 17.4 versus 14.6% respectively). Medical cancer patients demonstrated almost doubled ICU and hospital mortality rates (30.4 and 40.6% respectively) when compared with non-cancer medical patients (16.2 and 23.7% respectively). In the SOAP cohort ICU and hospital mortality amongst cancer patients were 20% and 27% respectively; of note, however, in this cohort 62.4% of cancer patients were admitted postoperatively [7]. In the Brazilian investigation by Soares et al, who unlike Taccone et al [7] did discriminate between planned and unplanned surgical ICU admissions, ICU and hospital mortality for cancer patients admitted for unplanned surgery were 23 and 37% respectively; medical cancer patients did much worse with ICU and hospital mortality of 44 and 58% respectively [8]. As such, the mortality rates reported in the current survey are much lower, which may be related to differences in selection for ICU admission and/or ICU care in Brazil and the Netherlands. Although stratification based on type of malignancy yielded relatively small subgroups, absolute numbers were sufficient to establish mortality rates in different cancer categories. This analysis showed that the prognosis of medical cancer patients admitted to the ICU is grim for all types of cancer. Multivariate analyses showed that amongst medical cancer patients with unplanned ICU admission respiratory tract cancer, upper gastrointestinal cancer or leukemia were associated with a higher mortality.

In the present analysis patients with a hematological malignancy demonstrated the highest ICU and hospital mortality rates: 42.8 and 53.2% respectively for patients with leukemia as their primary diagnosis versus 37.2 and 48.5% respectively for patients with lymphoma. These mortality rates in hematological patients, although very high, are lower than reported earlier (60%-70%) [13, 14]. It appears that the prognosis of hematological patients has improved over the years. This is in agreement with a study by Azoulay et al. who found by multivariable analysis, that admission after 1996 (compared with admission between 1990 and 1996) was associated with a better outcome in medical ICU-patients with cancer, mostly leukemia, lymphoma or myeloma patients [13].

Lung cancer was the most frequent solid tumor in our cohort of unplanned ICU admissions. In accordance, previous studies have documented that lung cancer is the most common solid tumor to require ICU admission, accounting for 16% of all cancer-related admissions [15]. As expected, mortality was much higher in medical patients with lung cancer than in surgical patients with this type of malignancy. [16]The ICU and hospital mortality of these patients was 33.5 and 48.6% respectively, which is in the same order of magnitude as reported previously [17]. Notably, studies published over the most recent 15 years demonstrate a clear trend toward improved survival of lung cancer patients admitted to the medical ICU [16].

While mortality is high for medical cancer patients, treatment cannot be considered futile based on cancer diagnosis alone. Even for patients with leukemia, the category with highest mortality in our study, the likelihood to survive up to the hospital discharge was almost 50%. Different prognostic models have been developed to more precisely predict the outcome of critically ill patients based on diagnosis, comorbidity and severity of illness. These general prognostic models were reported to underestimate the risk of dying for cancer patients admitted to the ICU [18]. However, most investigations that addressed the usefulness of general prognostic models in cancer patients requiring ICU care are limited by relatively small sample sizes and restriction to specific patients groups and/or specialized oncologic ICUs [19, 20].

Therefore, we here reported SMRs based on the APACHE IV model in our large cohort of cancer patients admitted to general ICUs. In contrast to earlier studies [18], we found lower mortality than predicted in most patient groups

In particular medical cancer patients presented with acute comorbid diseases more frequently than medical non-cancer patients. Acute comorbidity, not the long-term prognosis of the underlying malignancy, has been implicated as an important factor in mortality after a critical illness in cancer patients [21, 22]. A high proportion of medical cancer patients had confirmed infection. In accordance, severe sepsis is a common complication in cancer patients; the incidence of severe sepsis is four times higher in cancer than in non-cancer patients [23] and approximately 15% of septic shock patients have cancer or a hematologic malignancy [24]. Previous investigations have further indicated that clinically documented infections represent a frequent cause for ICU admission in cancer patients [21, 25, 26]. In addition, acute renal failure was relatively common in medical cancer patients, confirming previous smaller studies [12, 13].

A limitation of our study is that the type of malignancy is only recorded when cancer is the main reason for admission to the ICU; otherwise malignancy is scored as hematological malignancy or neoplasm/metastasized carcinoma without further specification. In addition, our data set does not provide information of the stage of cancer or chemotherapeutic regimens used. This is caused by the fact that data collection within the NICE registry does not focus specifically on cancer patients. As such, prospective investigations on the outcome of patients suffering from specific types and/or stages of cancer and/or treated with common chemotherapeutics remain of interest. Lastly, follow up of our patients was limited to hospital discharge. We cannot exclude that some patients may have died soon after hospital discharge, e.g. after discharge to a palliative care unit or hospice outside the medical institute with the ICU facility. This may lead to a too optimistic view on survival after ICU admission in cancer patients.

We here present the largest survey to date on the epidemiology and outcome of cancer patients on general ICUs. In a cohort of 140,154 critically ill patients with an unplanned ICU admission 10.9% had a diagnosis of a malignancy on admission. ICU and hospital mortality in medical cancer patients were almost twice as high as in medical patients without cancer, whereas differences in mortality amongst surgical cancer and non-cancer patients were modest. However even in patient groups with the highest mortality risk, survival up to hospital discharge was approximately 50%. These data indicate that the decision for unplanned ICU admission of cancer patients should take the different type of admission (medical versus surgical) on mortality risk into account. In addition, prospective studies examining the impact of the type and stage of malignancy, as well as previous therapies (e.g. different chemotherapeutic regimens and radiation), on ICU outcome are warranted to assist the oncology and ICU staff in the decision whether or not to admit a cancer patient to the ICU.

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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%, pancreatico-cholangiocarcimoma 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.

Table 1: Demographics

	All patients	Colorectal cancer surgery	Thoracotomy for lung cancer	CNS surgery for neo-plasm	Bladder cancer surgery	Esophageal cancer surgery	Renal cancer surgery	Pancreatico-cholangio-cancer surgery	Head and Neck cancer surgery	Female cancer surgery[2]	Male cancer surgery[1]	Other types of cancer
Number of patients	28,973	7,404	5,358	4,157	2,261	2,017	1,348	987	888	592	707	3,254
(%)	100	25.6	18.5	14.3	7.8	7.0	4.7	3.4	3.1	2.0	2.4	11.2
Gender (female) (%)	40	43	38	52	26	22	37	43	32	100	-	41
Planned admission (%)	77	68	80	89	79	84	73	73	82	61	64	80
Age (years)												
Median	67	74	66	57	68	64	68	67	63	68	67	67
Interquartile Ranges	59-75	65-80	59-72	46-66	62-74	58-71	60-75	60-73	56-71	58-77	62-72	58-75
Chronic comorbid disease (%)												
Chronic Obstructive Pulmonary Disease	10.6	11.4	20.0	3.1	7.8	9.8	10.2	6.6	11.8	10.1	9.9	7.0
Chronic renal insufficiency (+dialysis)	2.4	3.5	1.0	0.7	3.6	0.9	7.1	1.7	2.1	3.9	3.0	1.8
Heart failure	2.6	4.7	1.9	0.9	1.1	1.9	3.2	1.2	0.8	5.6	2.8	2.3
Cerebrovascular Accident	0.9	1.1	0.8	1.4	0.7	0.3	0.7	0.4	0.7	0.7	0.6	0.9
Immunodeficiency	9.9	12.1	5.7	6.4	6.4	22.4	5.6	2.2	9.6	9.6	3.8	16.8
Cirrhosis	0.4	0.5	0.3	0.1	0.3	0.6	0.2	0.5	1.1	0.5	0.1	0.8
Diabetes	11.1	15.1	8.1	5.8	10.4	11.8	14.5	19.6	8.6	13.5	9.5	10.8

[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	Pancreaticoduodenectomy-cholangiocancer 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 comorbidity[1] (%)												
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]	
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) *

*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. [1]Standard Deviation*

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

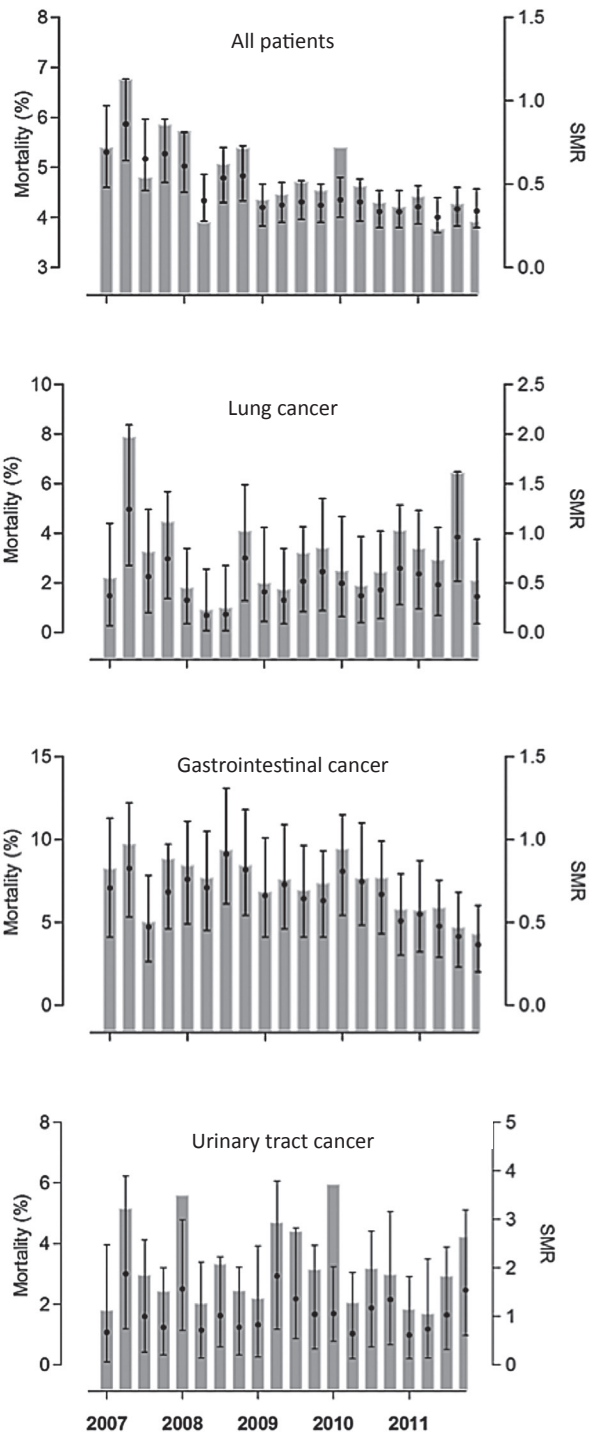
Background and main results

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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OUTCOME OF POSTOPERATIVE INTENSIVE CARE ADMISSION AFTER EMERGENCY COLORECTAL CANCER SURGERY DOES NOT DIFFER FROM OTHER EMERGENCY COLORECTAL SURGERY

CHAPTER 5

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Abstract

Background: Emergency presentation of colorectal carcinoma (CRC) is associated with a high morbidity and mortality, frequently requiring postoperative care on the intensive care unit (ICU). We here sought to determine whether CRC influences the short-term outcome of patients admitted to the ICU after emergency colorectal surgery.
Methods: We compared CRC patients who were admitted to the ICU after emergency colorectal surgery with a defined group of patients undergoing acute surgery for other colorectal diseases. We used the National Intensive Care Evaluation registry to identify all patients with unplanned admission to the ICU after emergency colorectal surgery between January 2007 and August 2012 in the Netherlands.
Results: 11,495 patients were admitted to the ICU after emergency colorectal surgery, of whom 13.7% had CRC. On ICU admission, CRC patients had a lower prevalence of confirmed infection (22.3%) than patients with non-malignant disease (41.0%). Patients with CRC had a shorter ICU length of stay (median 2.3 days) than patients without CRC (median 2.8 days). In addition, CRC patients had a lower ICU mortality (10.3 versus 12.9%). Hospital length of stay and mortality did not differ between groups. In a multivariate analysis in-hospital mortality was associated with high age, low body weight, high severity of illness at ICU admission, chronic comorbidities and metastasized carcinoma. CRC as reason for surgery, gender and organizational level of ICU were not associated with mortality.
Conclusion: The diagnosis of CRC does not influence in-hospital mortality of patients admitted to the ICU after emergency colorectal surgery.

Introduction

Colorectal cancer (CRC) is a common disease worldwide. In the United States CRC is the third most frequently diagnosed cancer and the second leading cause of cancer-related death [1]. In the Netherlands CRC is the second most common malignancy with an incidence of more than 57 per 100,000 population per year [2]. A subset of patients with CRC require acute surgery, e.g. after intestinal obstruction and/or perforation; the proportion of CRC patients with an acute presentation varied between 8-25% in different studies [3-6]. Acute presentation of CRC is associated with higher postoperative morbidity and mortality [5-9]. As a consequence, unlike after elective CRC operations, postoperative care after emergency CRC surgery is frequently provided on Intensive Care Units (ICUs).

We recently used the National Intensive Care Evaluation (NICE) registry, which prospectively collects data from all ICU admissions in 80 Dutch ICUs [10], to study the outcome of unplanned ICU admissions of 15,211 cancer patients in these ICUs during a four-year period [11]. In unplanned non-surgical cancer patients both ICU mortality and in-hospital mortality were almost twice as high as in unplanned non-surgical patients without cancer. In contrast, ICU mortality did not differ between unplanned surgical cancer patients and unplanned surgical non-cancer patients (9.0% and 8.9% respectively). In-hospital mortality was slightly higher in unplanned surgical cancer patients (17.4% and 14.6% respectively). This previous investigation did not stratify patients according to type of cancer or type of surgery [11].

Gender has been reported to influence treatments and outcome of patients with CRC [12]. Several studies have reported a longer survival of women after CRC resection when compared to men [12-15]. On the other hand, females with CRC more often present with an emergency, possibly because women undergo endoscopic screening less frequently than men [12, 15]. A possible gender effect on postoperative survival after emergency CRC surgery has not been studied thus far. Notably, gender may impact on the occurrence of complications and the type of therapeutic interventions while on the ICU. Although overall ICU mortality does not seem to differ between sexes [16, 17], men are more likely to develop sepsis [17-19]. Additionally, men are more likely to receive invasive therapeutic procedures while on the ICU [16, 20].

Knowledge of the short-term outcome of patients admitted to the ICU after emergency CRC surgery and how this relates to the outcome of patients receiving postoperative ICU care after unforeseen colorectal surgery for reasons not related to cancer is limited. We here sought to determine whether CRC is an important factor in the short-term outcome of patients admitted to the ICU after emergency colorectal surgery. Therefore, the specific aims of the present study were (1) to compare short-term outcomes of unplanned ICU admissions after emergency surgery for CRC with those in unplanned ICU admissions after emergency colorectal surgery for other reasons, and (2) to study factors that influence short-term outcomes in this acute CRC surgical population. For this we analyzed all ICU admissions in the Netherlands collected in the NICE registry from January 2007 through August 2012.

Methods

Ethics statement

The Dutch National Intensive Care Evaluation (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.

Patient data

The database of the NICE registry was used in this observational study [10]. In 1996 the NICE foundation started collecting data on patients admitted to Dutch ICUs. The participating ICUs (covering 80% of Dutch ICUs) provide information on all ICU admissions with the aim to assess and compare the performance of the ICUs and to improve the quality of care. For each ICU admission variables are collected that describe patient characteristics, severity of illness during the first 24 hours of ICU admission, and the ICU and in-hospital mortality and length of stay [10]. The data are encrypted such that all patient-identifying information, including name and patient identification number, are untraceable. The recorded variables are used to calculate probabilities of death for each patient using the Acute Physiology and Chronic Health Evaluation (APACHE) IV prognostic model [21]. Data for the current study were collected from all consecutive admissions to the 80 ICUs between January 1st 2007 and August 1st 2012. In the Netherlands, ICUs are categorized by organizational level 1, 2 or 3. Medical care is covered by certified intensivists for 24 hours per day, seven days per week in level 2 and 3 ICUs. The minimal volume of care per year is 3000 treatment days in level 3 and 1500 treatment days in level 2 ICUs. In level 1 ICUs, medical care is offered by intensivists at daytimes, while other medical specialists may be responsible at night and during weekends.

Selection of patients

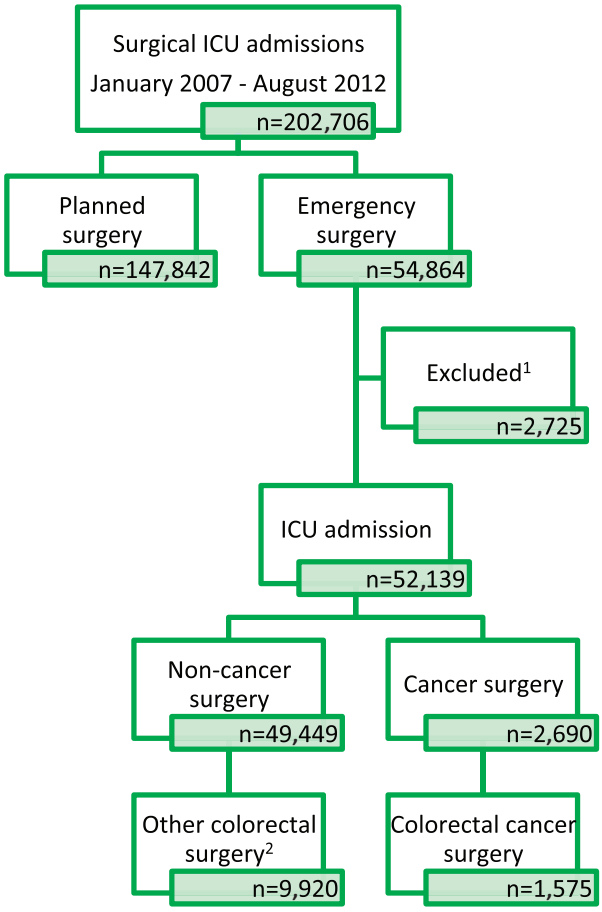
Patient selection was done according to Figure 1. Patients admitted to the ICU for emergency colorectal surgery were identified by selecting for (a) admission type (surgical and unplanned), (b) type of surgery (colorectal) and (c) indication (CRC or non-malignant disease, i.e. diverticular disease, fistula or abscess, gastrointestinal obstruction, perforation or rupture, or peritonitis). Patients with inflammatory bowel disease were excluded from the current analysis because they are likely to be younger and to use immune suppressive medication [22-24]; patients with gastrointestinal vascular ischemia were excluded because they are more likely to have significant comorbidities and a grim prognosis if acute surgery is needed [25-28]. In addition, surgery for complications of previous surgical procedures were excluded. 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, patients admitted after transplant operations (except for hepatic and renal transplantation) were excluded from the multivariate logistic regression analyses [21].

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 chi-squared test was used to compare categorical data, and the student's T test (for normally distributed variable) or Mann-Whitney U-test (non-normally distributed variables) were used for other variables when comparing two groups.

Type of colorectal surgery and outcome: to assess the associations between the type

Figure 1: Patient selection



Data were collected from all consecutive admission to 80 ICUs between January 1st 2007 and August 1st 2012.

[1] Excluded because ICU admission was done for logistical reasons (NICE registry definition: admission could have been postponed for 12 hours).

[2] Diverticular disease, fistula or abscess, gastrointestinal obstruction, perforation or rupture, or peritonitis.

of colorectal surgery, i.e. cancer vs. non-cancer, 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), gender, age (dichotomized as below or above 70 years), level of ICU, BMI (i.e. categorized as normal range, underweight and overweight), chronic comorbidities (i.e.

Table 1a: Patients admitted in the ICU after emergency colorectal surgery

	Colorectal Cancer Surgery 1,575 (13.7%)	Other Colorectal Surgery 9,920 (86.3%)	*p*
Age			
Median	74	71	
Interquartile Ranges	65-81	59-79	*<0.001*
<70 y (%)	37.6	46.3	*<0.001*
≥70 y (%)	62.4	53.7	*<0.001*
Mean BMI (SD)	**25.6 (8.3)**	**25.6 (6.1)**	***0.862***
Underweight (BMI <18.5) (%)	4.3	5.4	
Normal range (BMI 18.5-25.0) (%)	47.6	47.7	
Overweight (≥25.00) (%)	48.1	46.9	
Chronic comorbidity (%)			
Chronic renal failure[1]	4.1	7.2	*<0.001*
COPD	10.9	10.5	*0.456*
Heart failure	4.3	3.6	*0.088*
Diabetes	14.2	12.5	*0.031*
Neurologic disorder[2]	1.5	1.4	*0.655*
Cirrhosis	0.26	1.2	*<0.001*
Metastasized neoplasm	28.7	8.6	*<0.001*
Hematological malignancy	1.2	1.7	*0.085*
Level of ICU[3] (%)			***<0.001***
level 1	35.8	26.8	
level2	48.6	50.4	
level3	14.5	21.8	
Admission source[4] (%)			***<0.001***
Same Hospital	91.7	84.0	
Other hospital	6.8	14.3	

CRC = Colorectal cancer, [1] Includes chronic dialysis, [2] Includes previous cerebrovascular accident,
[3] Level one being lowest level and level three the highest level of ICU in the Netherlands, [4] Rest is missing.

COPD, Heart failure, neurologic disorder, neoplasm, and hematological malignancy), and acute comorbidities (i.e. confirmed infection, mechanical ventilation, vasopressors, and acute renal failure) were included in the model as covariates [21, 29].

Results were considered statistically significant if p-values were below 0.05. All statistical analyses were performed using PASW statistics 19 (SPSS, Chicago).

Results

Patients

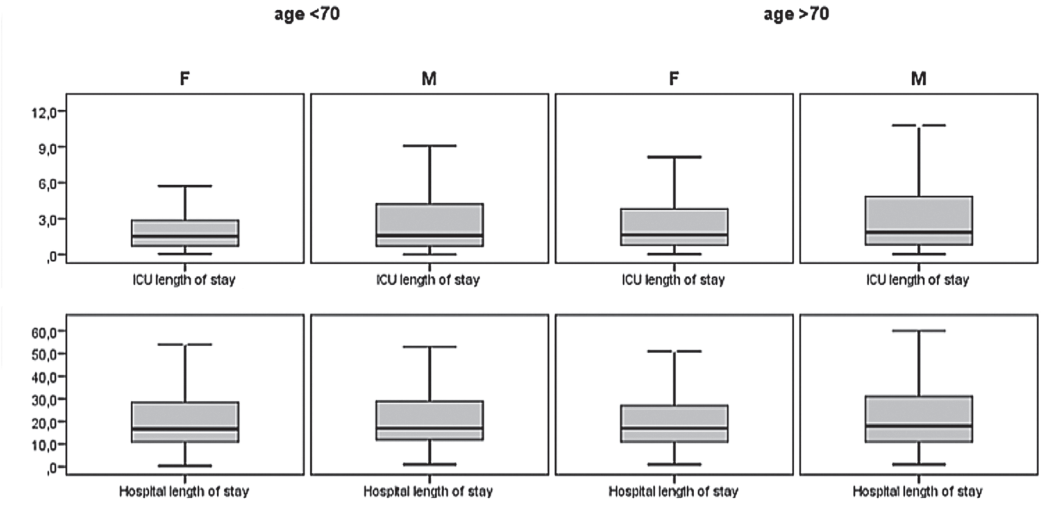
From January 2007 to August 2012, 11,495 patients were admitted to the participating ICUs after unplanned colorectal surgery (Figure 1, Table 1a). Of these, 1,575 (13.7%) had a diag-

nosis of CRC. Patients with CRC were older (median age 74 years) than patients admitted for unplanned colorectal surgery for non-malignant disease (median age 71 years) (p<0.001) and there were slightly more men in the former group (51.4% and 49.9% respectively, Table 1b). With regard to chronic comorbidity, differences between both patient groups were modest, with the CRC group harboring more patients with diabetes and fewer patients with chronic renal failure and cirrhosis. Of patients with CRC 28.7% had metastasized disease; notably, 8.6% of the unplanned colorectal surgical patients without CRC had a metastasized malignancy from another (not colorectal) origin. Patients with benign colorectal disease were more often admitted to the ICU from another hospital (14.3% versus 6.8% of patients with CRC, p<0.001). Both patient groups were predominantly admitted to a level 2 ICU; however, patients with benign colorectal disease more often were admitted to a level 3 ICU when compared with patients with CRC.

Acute comorbidity and admission laboratory results

Clear differences existed between patient groups with regard to acute comorbidity (Table 2a). Patients undergoing emergency surgery for other reasons than CRC had a higher prevalence of confirmed infection and sepsis (both p<0.001 versus CRC patients), more frequently had acute renal failure (p<0.001), and more often required mechanical ventilation (p<0.001) and vasopressors (p=0.007). APACHE IV scores were similar in both patient-groups (Table 2a). With regard to laboratory results on the first day after admission, differences between groups were

Figure 2: ICU and hospital length of stay for unplanned CRC patients admitted to the ICU for emergency colorectal surgery stratified according the age (< 70 and > 70 years) and gender



Data are expressed as box-and-whisker diagrams depicting the smallest observation, lower quartile, median, upper quartile and largest observation.

Table 1b: Patients admitted in the ICU after emergency colorectal surgery separated by gender

	Colorectal Cancer Surgery			Other Colorectal Surgery		
	Female 765 48.6%	Male 810 51.4%	*p*	Female 4,968 50.1%	Male 4,952 49.9%	*p*
Age						
Median	76	72	*<0.001*	74	69	*<0.001*
Interquartile Ranges	66-83	64-80		61-81	58-77	
<70 y (%)	32.4	42.8	*<0.001*	40.4	52.2	*<0.001*
≥70 y (%)	67.6	57.2	*<0.001*	59.6	47.8	*<0.001*
Mean BMI (SD)	**25.5 (6.7)**	**25.7 (9.7)**	***0.831***	**25.8 (6.5)**	**25.5 (5.6)**	***0.614***
Underweight (BMI <18.5) (%)	6.3	2.5		6.7	4.1	
Normal range (BMI 18.5-25.0) (%)	46.6	48.5		45.8	49.7	
Overweight (≥25.00) (%)	47.1	49.0		47.5	46.2	
Chronic comorbidity (%)						
Chronic renal failure[1]	3.2	4.9	*0.138*	6.1	8.2	*<0.001*
COPD	9.2	12.5	*0.035*	10.0	11.0	*0.001*
Heart failure	3.5	5.1	*0.139*	3.4	3.8	*0.171*
Diabetes	13.5	14.9	*0.428*	13.7	11.3	*<0.001*
Neurologic disorder[2]	1.6	1.5	*0.525*	1.3	1.5	*0.494*
Cirrhosis	0.1	0.4	*0.625*	1.0	1.3	*0.103*
Metastasized neoplasm	28.8	28.6	*1.000*	7.8	9.4	*0.002*
Hematological malignancy	0.8	1.5	*0.239*	1.3	2.0	*0.003*
Level of ICU[3] (%)			***0.066***			***0.010***
level 1	35.8	35.7		28.4	25.1	
level2	47.5	49.6		50.3	50.5	
level3	16.3	13.3		20.5	23.2	
Admission source[4] (%)			***0.165***			***0.398***
Same Hospital	91.4	92.0		84.3	83.7	
Other hospital	7.6	6.0		13.8	14.7	

[1] Includes chronic dialysis, [2] Includes previous cerebrovascular accident, [3] Level one being lowest level and level three the highest level of ICU in the Netherlands, [4] Rest is missing.

modest at best and clinically not relevant (Table 2a). In accordance with the higher prevalence of acute renal failure in patients undergoing emergency surgery for other reasons than CRC, peak plasma creatinin levels were higher in this group than in patients with CRC (Table 2a, p<0.001).

Length of stay and mortality

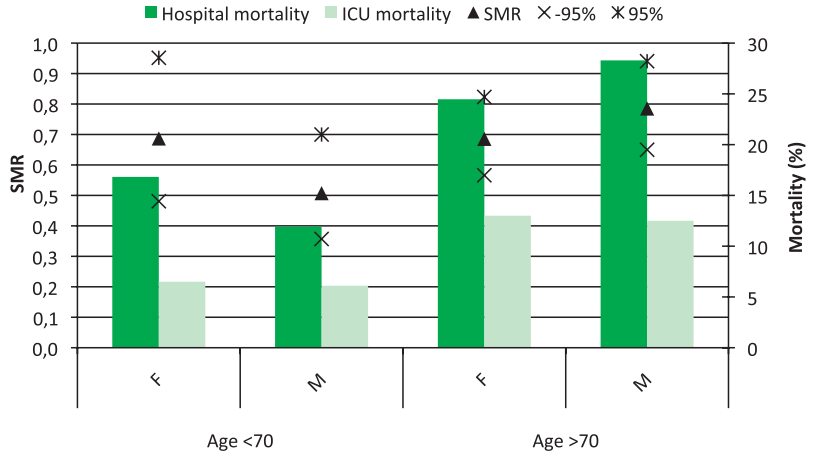
Patients with CRC had a shorter length of stay on the ICU (median 2.1 days) than patients with benign colorectal disease (median 2.8 days)(p<0.001), while hospital length of stay did not

differ between patient groups (median 19 days, Table 2a). Similarly, patients with CRC had a lower ICU mortality (10.3% vs 12.9%, p=0.004), whereas in-hospital mortality was not different between groups (22.5 and 21.7% respectively, p=0.523). Multivariate analysis showed that high APACHE IV score, high age, low body weight, COPD, chronic heart failure, metastasized carcinoma, hematologic malignancy, mechanical ventilation, treatment with vasopressors and acute renal insufficiency were all independently associated with in-hospital mortality (Table 3). On the other hand, surgery for CRC and organizational level of the ICU were not associated with in-hospital mortality.

Influence of gender

To obtain insight into a possible influence of gender on the outcome of emergency colorectal surgery in cancer patients, we studied differences between males and females in this group and (as a reference) in the group of non-CRC unplanned surgery (Tables 1b, 2b). Severity of illness, age, body weight index and acute and chronic co-morbidities were comparable in male and female patients. In patients without cancer, but not in CRC patients, ICU mortality and in-hospital mortality were higher in female patients. In the multivariate analysis, gender was not associated with in-hospital mortality (Table 3). Considering that women were relatively older than men in both patient groups (Table 1b), we also determined ICU and hospital length of stay in men and women with CRC aged below or above 70 years admitted for unplanned colorectal surgery (Figure 2). Clearly, gender did not influence length of stay in either age cohort. Finally, we assessed the impact of gender on ICU and hospital mortality in CRC patients stratified according to age (below or above the age of 70; Figure 3). This analysis showed that older

Figure 3: ICU and hospital mortality of unplanned CRC patients admitted to the ICU for emergency colorectal surgery stratified according the age (< 70 and > 70 years) and gender



CRC = Colorectal cancer. Bars indicate hospital mortality (dark green) and ICU mortality (light green). Triangles indicate SMR (standardized mortality ratio) with 95% confidence intervals.

Table 2a: Admission parameters, severity of illness and mortality for patients admitted in the ICU after emergency colorectal surgery

	Colorectal Cancer Surgery (1,575)	Other Colorectal Surgery (9,920)	*p*
Acute comorbidity (%)			
GI bleeding	1.7	1.2	*0.098*
Confirmed infections	22.3	41.0	*<0.001*
Pneumonia	1.4	1.2	*0.333*
Sepsis	9.2	19.6	*<0.001*
CPR	0.8	0.8	*0.515*
Cardiac dysrhythmia	8.2	8.4	*0.437*
Vasopressors	42.8	46.1	*0.007*
Immunodeficiency	4.7	8.2	*<0.001*
Mechanical ventilation 24hrs	51.8	61.3	*<0.001*
Acute renal failure	7.3	12.2	*<0.001*
Laboratory results day 1 (Median and IQR)			
Hematocrit (lowest, liter/liter)	0.29 (0.25-0.34)	0.30 (0.25-0.34)	*0.797*
Leukocytes (highest $x10^9$/liter)	11.5 (11.9-17)	11.6 (7.4-17)	*0.902*
Leukocytes (lowest $x10^9$/liter)	8.2 (4-12.5)	8.4 (4.4-13.1)	*0.003*
Thrombocytes (lowest $x10^9$/liter)	230 (157-299)	204 (141-292)	*<0.001*
Albumen (lowest gram/liter)	17 (12-22)	18 (12-23)	*0.566*
Creatinin (max, micromole/liter)	87 (66-126)	99 (70-152)	*<0.001*
PaO2/FiO2 ratio	254 (186-337)	236 (168-320)	*<0.001*
Severity of illness and mortality			
APACHE IV score (IQR)	70 (54-88)	69 (57-87)	*0.616*
ICU lengths of stay (IQR)	2.1(0.9-5.7)	2.8 (1.1-7.4)	*<0.001*
Hospital length of stay (IQR)	19 (12-32)	19 (11-35)	*0.359*
ICU mortality (%)	10.3	12.9	*0.004*
Hospital mortality (%)	21.7	22.5	*0.523*
APACHE IV SMR (±95% CI)	0.69 (0.57-0.81)	0.91(0.81-1.01)	*<0.001*

IQR = Interquartile ranges

patients of both genders had a significantly higher ICU and hospital mortality. Most notably, whereas ICU mortality was similar in men and women in both age cohorts, hospital mortality was lower in men aged below 70 years but higher above 70 years when compared to women within the respective age cohorts.

Discussion

To the best of our knowledge our study is the first to specifically address postoperative care and outcome of CRC patients who are admitted to the ICU after emergency colorectal surgery. Our survey comprised 1,575 CRC patients who received postoperative care in one of 80 partici-

pating ICUs after unplanned surgery during a five-year and seven-month period, and who were compared with 9,920 patients who received postoperative care after unplanned colorectal surgery for other reasons during the same period in the same ICUs. Our main findings are that CRC patients had fewer acute comorbidities, fewer infections, a shorter length of ICU stay and a lower ICU mortality, while hospital length of stay and mortality did not differ between groups. In accordance, in a multivariate analysis, low body weight, high age, chronic comorbidities and high severity of illness at ICU admission, but not CRC, gender or organizational level of ICU were associated with in-hospital mortality.

In spite of improved surgical techniques and perioperative care colorectal surgery remains to account for the greatest share of adverse events in general surgical patients, contributing a disproportionate part of morbidity, mortality and length of stay in this group [30]. Postoperative complication rates and mortality after CRC surgery are as high as 20-40% and 5% respectively [31-34]. Emergency surgery for CRC bears an even greater risk for postoperative complications and mortality. In a Dutch study, the risk of developing any postoperative complication among colon cancer patients was significantly higher for those undergoing emergency surgery (odds ratio 3.6) [35]. Similarly, emergency surgery was identified as an important risk factor for mortality amongst CRC patients, bearing a 2.5-fold increased risk of death [34]. Moreover, in an investigation that examined > 30,000 colorectal resections in 142 US hospitals mortality was 1.9% after nonemergency surgery versus 15.3% after emergency operations [36]. In accordance, in our cohort of patients after unplanned CRC surgery, we found high ICU mortality and in-hospital mortality of 10% and 22% respectively. Importantly, the high mortality was also found in patients after unplanned colorectal surgery for non-cancer diagnoses.

Our findings differ from a previous study comparing outcome of Dutch patients after unplanned ICU admission for cancer versus non-cancer reasons [11]. In that study medical cancer patients had a strongly increased hospital mortality (40.6%) when compared with medical non-cancer patients (23.7%); mortality was also higher in unplanned surgical patients with cancer compared with surgical patients without cancer (17.4% vs. 14.6%) [11]. This earlier study contained all types of cancer [11]. In the current analysis in patients with CRC only, the risk of mortality was not higher in patients with cancer as compared with patients with non-cancer reasons for colorectal surgery requiring ICU admission, such as treatment for diverticular disease, fistula, abscesses, gastrointestinal obstruction, perforation or rupture. Interestingly, ICU mortality was even lower in patients with CRC compared with patients after colorectal surgery for other reasons. This lower mortality may be explained by higher acute comorbidities, such as infections and renal failure, in patients admitted to the ICU after non-cancer surgery.

Based on earlier studies, we hypothesized that gender could have an important influence on outcome after CRC surgery [12-15]. Also, gender has been shown to affect ICU care [16, 20, 37]. A large population-based study conducted in Canada demonstrated that older women with critical illness were less likely than critically ill men to be admitted to an ICU and were more likely to die in the ICU or hospital [20]. A prospective study involving 25,998 adult patients admitted to 31 ICUs in Austria also documented gender-related differences in ICU care, with male patients - despite presenting with a lower severity of illness - more likely than female patients to receive a high level of care, as defined by the number of invasive procedures [16]. Although in this investigation women had a higher observed mortality rate than men, there was no difference in outcome after adjustment for the severity of illness [16]. Overall ICU mortality did not differ between sexes in another study [17]. In our current study gender did not impact on

Table 2b: Admission parameters, severity of illness and mortality for patients admitted in the ICU after emergency colorectal surgery separated by gender

	Colorectal Cancer Surgery			Other Colorectal Surgery		
	Female (765)	Male (810)	*p*	Female (4,968)	Male (4,952)	*p*
Acute comorbidity (%)						
GI bleeding	1.4	1.9	*0.558*	0.7	1.7	*<0.001*
Confirmed infections	23.0	21.7	*0.546*	41.1	41.0	*0.439*
Pneumonia	1.2	1.6	*0.524*	1.0	1.4	*0.058*
Sepsis	9.0	9.4	*0.862*	19.6	19.5	*0.501*
CPR	1.0	0.6	*0.411*	0.8	0.8	*0.539*
Cardiac dysrhythmia	8.0	8.4	*0.783*	8.2	8.5	*0.301*
Vasopressors	43.7	41.9	*0.476*	46.1	46.1	*0.489*
Immunodeficiency	4.1	5.3	*0.284*	8.0	8.4	*0.240*
Mechanical ventilation 24hrs	51.2	52.3	*0.687*	61.0	61.5	*0.297*
Acute renal failure	7.1	7.4	*0.846*	11.9	12.5	*0.179*
Laboratory results day 1 (Median and IQR)						
Hematocrit (lowest, liter/liter)	0.29 (0.26-0.32)	0.29 (0.26-0.33)	*0.366*	0.29 (0.25-0.32)	0.30 (0.26-0.34)	*0.614*
Leukocytes (highest x10^9/liter)	11.6 (8.7-17)	10.5 (6.9-14.7)	*0.380*	11.8 (7.6-17)	11.5 (7.4-16.7)	*0.334*
Leukocytes (lowest x10^9/liter)	8.4 (4.3-12.5)	8.0 (4.0-11.1)	*0.032*	8.4 (4.4-13.1)	8.3 (4.4-12.7)	*0.669*
Thrombocytes (lowest x10^9/liter)	236 (164-299)	223 (157-293)	*0.099*	212 (150-292)	196 (141-280)	*<0.001*
Albumen (lowest gram/liter)	16 (12-20)	18 (14-22)	*0.013*	17 (12-21)	18 (14-23)	*0.001*
Creatinin (max, micromole/liter)	76 (59-108)	97 (74-139)	*<0.001*	87 (63-137)	110 (78-169)	*<0.001*
PaO2/FiO2 ratio	256 (186-350)	252 (185-329)	*0.140*	240 (170-327)	232 (166-311)	*0.001*
Severity of illness and mortality						
APACHE IV score (IQR)	72 (58-88)	67 (56-83)	*0.373*	70 (55-89)	69 (53-86)	*0.023*
ICU lengths of stay (IQR)	2.0 (0.9 -5.6)	2.5 (0.9 -5.8)	*0.061*	2.7 (1.0 -7.1)	2.8 (1.1 -7.5)	*0.225*
Hospital length of stay (IQR)	18 (11-30)	18,3 (12 -35)	*0.120*	19 (10-35)	20 (11-36)	*0.275*
ICU mortality (%)	10.8	9.8	*0.507*	14.4	11.4	*<0.001*
Hospital mortality (%)	22.1	21.3	*0.706*	24.5	20.4	*<0.001*
APACHE IV SMR (±95% CI)	0.68 (0.58-0.80)	0.69 (0.59-0.81)	*ns*	0.95 (0.89-1.01)	0.87 (0.81-0.93)	*ns*

IQR = Interquartile ranges, l.o.s. = length of stay, SMR = standardized mortality ratio

Table 3: Multivariate analysis for hospital mortality

	Odds ratio (CI)
Colorectal Cancer admission	0.87 (0.73-1.03)
Male	1.08 (0.96-1.22)
Age ≥ 70 years	2.41 (2.11-2.74)
APACHE IV score	1.03 (1.02-1.04)
Level of ICU	
Level 1	1.00
Level 2	0.89 (0.75-1.05)
Level 3	1.05 (0.91-1.22)
BMI	
Underweight (BMI <18.5)	1.36 (1.22-1.55)
Normal range (BMI 18.5-25.0)	1.00
Overweight (≥25.00)	0.84 (0.75-0.99)
Chronic comorbidities	
COPD	1.52 (1.29-1.80)
Heart failure	1.74 (1.33-2.30)
Neurologic disorder	1.42 (0.91-2.15)
Metastasized neoplasm	1.94 (1.65-2.29)
Hematological malignancy	1.67 (1.14-2.43)
Acute comorbidities	
Confirmed infection	1.03 (0.93-1.18)
Mechanical ventilation 24hrs	1.39 (1.25-1.66)
Vasopressors	1.31 (1.15-1.50)
Acute renal failure	1.47 (1.25-1.73)

CI = 95% Confidence Interval

ICU or hospital mortality after unplanned ICU admission following emergency CRC surgery.
Our study has some limitations. We extracted data from the NICE registry, which collects data from all ICU admissions to 80 general ICUs in the Netherlands. NICE primarily monitors the performance of ICUs and does not focus specifically on cancer patients. As a consequence thereof, the type of malignancy is only recorded when cancer is the main reason for admission to the ICU; otherwise malignancy is scored as hematological malignancy or metastasized carcinoma without further specification. Hence, the current analysis involves patients of whom CRC was considered one of the maximal two recorded main admission diagnosis by the treating ICU physician. Our study is also limited by the fact that we cannot evaluate the impact of the stage of CRC, which is a major denominator of one-year mortality after colorectal surgery [34], on immediate postoperative outcome, since this information is not collected in the NICE data base. In addition, our survey is limited in that patient follow up was restricted to hospital discharge. Of note, however, the objective of our study was to evaluate the direct outcome of ICU postoperative care after emergency colorectal surgery (i.e. not the impact of emergency CRC surgery on cancer progression and outcome); hence, although we cannot exclude that some

patients died soon after hospital discharge, this limitation in follow up is unlikely to influence our results to an important extent. Finally, a limitation of our study is that we only analyzed the outcome of patients after emergency colorectal surgery who received postoperative care on the ICU. Mortality may differ in patients after unplanned colorectal surgery for CRC or other types of colorectal surgery not requiring ICU admission.

We excluded patients with IBD or ischemic colitis from the reference group receiving postoperative care after emergency colorectal surgery for benign disease, since they differ considerably from CRC patients in various aspects. The proportion of IBD patients going to the ICU is low, many use immune suppressive therapy and the age-peak of incidence of IBD differs strongly from the average age of CRC patients [22-24]. Patients with ischemic colitis have significant comorbidities and are usually treated in a conservative way; if surgery is deemed necessary the outcome is poor with postoperative mortality rates of 37-47%, which at least in part is caused by the underlying widespread vascular occlusive disease rather than by the extent and the complexity of the surgical procedure [25-28]. As such, patients undergoing emergency colorectal surgery for IBD or ischemic colitis are not suitable comparators for patients undergoing unforeseen colorectal surgery for CRC.

In conclusion, we here report that ICU and hospital mortality amongst CRC patients admitted to the ICU after emergency colorectal surgery for all causes is 10.3% and 21.7% respectively. While ICU mortality is slightly lower amongst CRC patients when compared to patients after emergency colorectal surgery for non-malignant disease, hospital mortality is similar in both groups. Factors associated with mortality include high age, low body weight, high severity of illness at ICU admission, chronic comorbidities and metastasized carcinoma. In addition, we show that gender does not influence postoperative outcome after unplanned ICU admission for emergency colorectal surgery. While in the early 1980s the presence of a malignancy was considered a contraindication for admission to an ICU, the success of anti-cancer therapies has created a mind switch amongst clinicians with regard to the use of aggressive supportive therapy in cancer patients [38, 39]. The current study adds to this growing evidence, showing that the diagnosis of CRC should not influence the decision whether or not to provide postoperative ICU care after emergency colorectal surgery.

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BLOODSTREAM INFECTIONS IN PATIENTS WITH OR WITHOUT CANCER IN A LARGE COMMUNITY HOSPITAL

CHAPTER 6

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Infection (accepted for publication)

Abstract

Purpose: Cancer is associated with an increased risk to acquire bloodstream infection (BSIs). Most knowledge on pathogens and outcome of are derived from specialized cancer centres. We here sought to compare causative microorganisms in BSIs in patients with or without cancer in a 600-bed teaching community hospital.
Methods: We analysed all positive blood cultures from adult patients between January 2005 and January 2011.
Results: 4,918 episodes of BSI occurred in 2,891 patients, of whom 13.4% had a diagnosis of cancer (85.5% with a solid tumour). In both patient groups Gram-positive isolates were more prevalent (58.7 and 61.4% in patients with and without cancer respectively) than Gram-negative isolates (31.8 and 32.3% respectively). Amongst Gram-positive organisms, coagulase negative staphylococci, *Staphylococcus (S.) aureus* and enterococci were most frequently isolated in both patient groups; in cancer patients twice as many BSIs were caused by *Enterococcus (E.) faecalis* and *E. faecium*. Amongst Gram-negative organisms, *Escherichia (E.) coli* was the most common isolate; in cancer patients twice as many BSIs were caused by *Pseudomonas aeruginosa* and *Enterobacter cloacae*. Yeasts were grown from 3.0% of blood cultures from cancer patients versus 1.5% of cultures from non-cancer patients. Cancer patients had a 90-day mortality of 35.8% following BSI versus 23.5% in patients without cancer.
Conclusion: These data demonstrate distinct BSI pathogens and impaired outcomes in patients with cancer in the setting of a large community teaching hospital.

Introduction

Bloodstream infections (BSIs) represent a major cause of morbidity and mortality in cancer patients [1-3]. Cancer is associated with a strongly increased risk to acquire BSI [4-6]. In accordance, cancer is the most common comorbid condition in patients with sepsis, reported to be present in approximately 17% of cases [7, 8]. Cancer patients are more vulnerable to develop invasive infection due to various reasons, including an often progressive catabolic state, ulcerating lesions in mucosal surfaces and immune suppression secondary to chemotherapy, radiation, immune modulating therapeutics and/or the malignancy itself [9]. Patients with neutropenia are particularly prone to develop BSI, with the highest risk for patients who have undergone bone marrow transplantation [3, 10-12]. BSIs not only cause considerable mortality, but also prolong hospital stay and increase patient care costs [13].

Until the 80s, Gram-negative bacteria were the most common cause of BSIs in the western world. Since then, Gram-positive organisms have become increasingly frequent as causative agents of BSIs [5, 8, 14]. In addition, the proportion of *Candida* species among BSI isolates has increased in recent decades [5, 8]. In a large survey involving 2,340 cancer patients studied between 1995 and 2001 Gram-positive organisms accounted for 62% of all nosocomial BSIs in 1995 and for 76% in 2000, whereas Gram-negative organisms accounted for 22% and 14% of all BSIs for these years, respectively; the predominant pathogens were coagulase-negative staphylococci [12]. Other investigations have examined the causative agents implicated in BSIs in cancer patients in specialized cancer centres and/or specific cancer populations, such as patients with haematological malignancies, neutropenia and/or after bone marrow transplantation [3, 15-18]. In the Netherlands most cancer patients are treated in community hospitals. The primary objective of the current study was to obtain insight into the distribution of pathogens causing BSI in cancer patients (as compared with patient without malignancy) in the setting of a community teaching hospital. For this we analysed all positive blood culture results obtained in our institution from adult patients between January 2005 and January 2011. We report blood culture isolates, resistance patterns, demographics , referring specialties, type of cancer, cancer treatments and outcome.

Materials and Methods

Patient and design

This study is a single centre retrospective analysis of all positive blood culture results obtained from adult patients (> 16 years of age) between January 2005 and January 2011 registered in a 600-bed community teaching hospital in the Netherlands (Reinier de Graaf Hospital, Delft). For this study, BSIs were diagnosed solely on the basis of at least one positive blood culture irrespective of the causative microorganism. Multiple positive blood cultures with the same microorganism in the same patient within a 24-hour time frame were considered as a single positive blood culture. Positive blood cultures were identified in the hospital microbiology information system (General Laboratory Information Management System, GLIMS®, MIPS Diagnostics Intelligence, Gent, Belgium). Identification numbers of patients with a positive blood culture were linked with (a) the hospital patient registration system containing encoded "diagnosis and treatment combinations" (a nationwide coding and registration system for all patients entering a hospital, either as outpatient or inpatient, providing information about the

diagnosis and treatment specified by the attending physician), and (b) the hospital laboratory information system (GLIMS), containing data on routine laboratory tests. Laboratory test results were included in the analysis if obtained in the period from 24 hours before to 48 hours after the blood culture was taken. Information about all-cause mortality, also after hospital discharge, was collected from the hospital information system.

Blood cultures

Blood was routinely inoculated into two separate bottles for aerobic and anaerobic culture respectively (Becton-Dickinson, Breda, the Netherlands; 10 mL each). All cultures were processed in a Bactec 9000-seriescontinuous monitoring system (Becton-Dickinson) and incubated until microbial growth was detected or for four days; incubation periods were longer in case of suspected endocarditis or infection with *Legionella* or yeasts. Isolates from positive bottles were mostly identified by standard methods using the Phoenix 100 system(Becton-Dickinson) or API-methodology (bioMérieux, Lyon, France). Antimicrobial susceptibility testing was done with a Phoenix Automated Microbiology System (BD Diagnostics, USA) or disk diffusion with breakpoint criteria according to Clinical and Laboratory Standards Institute (CLSI) guidelines.

Statistical analysis

Data are shown as medians with interquartile ranges unless indicated otherwise. Differences between groups were analysed by Mann-Whitney U tests. Survival data were analysed by log-rank (Mantel Cox) and Chi-square tests. A p value < 0.05 was considered statistically significant. The analyses were performed using Statistical Package for the Social Sciences version 20 (SPSS, Chicago, IL).

Results

Patients

In the six-year study period, 4,918 microorganisms were cultured from a total of 4,196 positive blood cultures in 2,891 patients (Table 1). Of these 386 patients (13.4%) had a diagnosis of cancer. The vast majority of cancer patients had a solid tumour (330 or 85.5%, versus 56 or 14.5% with a hematologic malignancy, Table 2). When compared with patients without a malignancy, cancer patients were more frequently male (61.4% versus 51.8%); the age distribution was similar between groups. The hospital locations where positive blood cultures were obtained differed considerably between cancer and non-cancer patients, although in both patient groups most cultures were acquired in non-surgical departments (31.1% and 43.1% in cancer and non-cancer patients respectively, Table 1). The proportion of (positive) blood cultures taken in the emergency room or non-surgical departments was higher in patients without cancer, whereas the fraction of blood cultures drawn in the intensive care unit and surgical departments was higher in patients with cancer.

Pathogens

Table 3 shows blood culture isolates in patients with and without cancer. In both patient groups Gram-positive isolates were more prevalent (58.7 and 61.4% in patients with and without cancer respectively) than Gram-negative isolates (31.8 and 32.3% respectively). Amongst Gram-positive organisms, coagulase negative staphylococci *Staphylococcus (S.) aureus* and en-

Table 1: Demographic characteristics of all patients with blood stream infections

		Cancer			Non-cancer		*p*
Number of patients (%)		386	(13.4)		2,505	(86.4)	-
Number of positive cultures		765			4,153		-
Mean age in years (IQR[1])		69	(61-76)		70	(52-80)	*ns*
Male (%)		237	(61.4)		1,299	(51.8)	*<0.01*
Number of CVC[2] with positive cultures (%)		119	(30.8)		382	(15.2)	*<0.01*
Location cultures were drawn (%)							
Emergency Room		121	(15.8)		1,047	(25.2)	*<0.01*
Intensive Care Unit		100	(13.1)		257	(6.2)	*<0.01*
Surgical departments[3]		168	(22.0)		500	(12.0)	*<0.01*
Non-surgical departments[4]		238	(31.1)		1,789	(43.1)	*<0.01*
Other		138	(18.0)		560	(13.5)	*<0.01*
Laboratory results †, *data are given as median (IQR[1])*							
Data are given as median (IQR[1])	#			#			
Hemoglobin (mmol per liter)	286	6.2	(5.5-7.1)	1,579	7.0	(5.9-8.1)	*<0.01*
White blood count (x 10^9 per liter)	278	11.4	(5.8-16.2)	1,575	12.2	(8.7-17.2)	*0.02*
Neutrophils (x 10^9 per liter)	205	10.0	(6.8-14.2)	1,357	9.9	(6.7-14.4)	*0.90*
Absolute neutrophil count < 1x10^9 per liter	196	9	(4.6%)	1,357	26	(1.9%)	*0.03**
Thrombocytes (x 10^9 per liter)	270	200	(99-326)	1,520	209	(144-280)	*0.40*
Creatinin (micromole per liter)	273	85	(65-112)	1,487	100	(76-158)	*<0.01*
Prothrombin Time (seconds)	126	16.0	(15.2-17.1)	614	16.3	(14.9-18.4)	*0.40*
C-Reactive Protein (milligram per liter)	238	143	(76-219)	1,379	128	(61-208)	*0.20*
Albumin (gram/liter)	212	22	(17-30)	1,180	27	(21-34)	*<0.01*
Glucose (mmol/liter)	105	7.4	(6.1-8.6)	774	7.1	(6.0-8.9)	*0.20*

[1] *Interquartile range*

[2] *Central Venous Catheter*

[3] *Including department of surgery, gynecology, urology, ENT, and orthopedics*

[4] Including department of medicine, gastro-enterology, pulmonology, neurology, cardiology

 # Number of samples tested

** By Chi-square*

† Laboratory results drawn minus 24 hours or plus 48 hours after blood culture was taken

terococci were most frequently isolated in both patient groups. However, within the group of Gram-positive isolates differences existed between patients with and without malignancy: in cancer patients with positive blood cultures, *Enterococcus (E.) faecalis* and *E. faecium* were twice as common when compared with non-cancer patients, while patients without malignancy had almost five times as many positive cultures for haemolytic streptococci. Amongst Gram-negative organisms, *Escherichia (E.) coli* was the most common isolate in both patient groups. Notably, P*seudomonas (P.) aeruginosa* and *Enterobacter (E.) cloacae were twice as common in patients with cancer* whereas *E. coli* was cultured more frequently from patients without cancer. Yeasts were grown from 3.0% of positive blood cultures from cancer patients

Table 2: Type of malignancy and treatment in cancer patients with positive blood cultures

Type of cancer	patients (%) n=386
Lung cancer	28 (7.3)
Colorectal cancer	74 (19.2)
Pancreaticobilliary cancer	63 (16.3)
Esophageal/Gastric cancer	35 (9.1)
Prostate cancer	23 (6.0)
Other urinary tract cancer	53 (13.7)
Breast cancer	31 (8.0)
Gyneacological cancer	11 (2.8)
Melanoma	3 (0.8)
Head and Neck cancer	3 (0.8)
CNS malignancy	3 (0.8)
Other	3 (0.8)
Leukemia[1]	24 (6.2)
Malignant lymphoma	32 (8.3)
Type of treatment	
Surgery	56 (14.5)
Radiation therapy	9 (2.3)
Chemotherapy	99 (25.6)
Hormonal Therapy[2]	10 (2.6)
Endoscopic procedures[3]	120 (31.1)
Other /no treatment	92 (23.8)

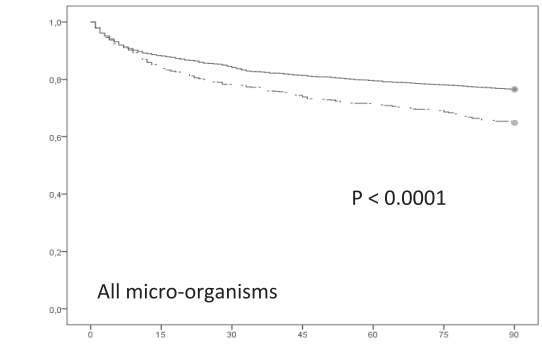
[1] *Includes acute and chronic leukemia*
[2] *Includes tamoxifen, aromatase-inhibitors, LH-RH and anti-androgenic therapy*
[3] *includes cystoscopy, hysteroscopy, colonoscopy, gastroscopy, and bronchoscopy.*

versus 1.5% of cultures from non-cancer patients; this difference was caused by a higher incidence of *Candida non-albicans* species in cancer patients. In 502 patients who had a central venous catheter (119 patients with cancer and 382 non-cancer patients), 919 pathogens were cultured (Table 4); in patients with cancer, positive blood cultures more often yielded Gram-negative bacteria, in particular *P.aeruginosa*, while coagulase negative staphylococci were more common in non-cancer patients. In Table 5 susceptibility patterns for the most relevant micro-organisms are enlisted. Only meropenem resistance of *P.aeruginosa* was higher in cancer patients. All other antimicrobial resistance patterns did not significantly differ between cancer and non-cancer patients.

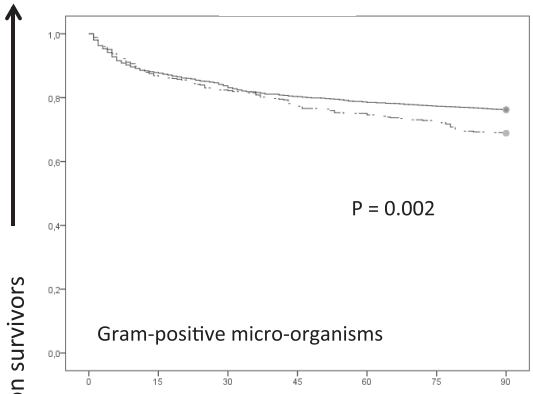
Laboratory results

Laboratory results at the time of blood cultures are shown in Table 1. Cancer patients had lower haemoglobin levels and white blood cell counts; Cancer patients also had lower plasma creatinin and albumin concentrations. C-reactive protein levels did not differ between groups. Blood culture isolates in neutropenic patients are shown in Table 6.

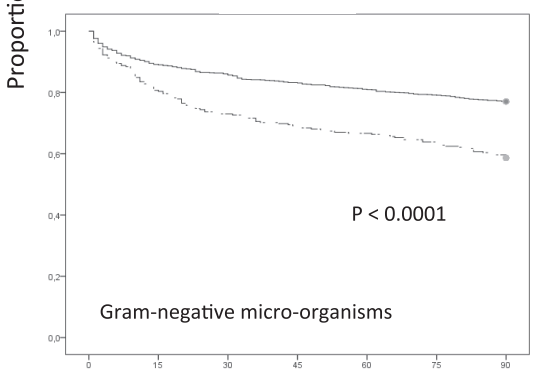
Figure 1: Survival for cancer and non-cancer patients



All types of micro-organisms	cancer	non-cancer
7 days	0.91	0.91
30 days	0.78	0.84
60 days	0.71	0.80
90 days	0.65	0.77



Gram-positive micro-organisms	cancer	non-cancer
7 day	0.92	0.91
30 day	0.82	0.83
60 days	0.75	0.79
90 days	0.69	0.76



Gram-negative micro-organisms	cancer	non-cancer
7 days	0.89	0.92
30 days	0.73	0.86
60 days	0.67	0.81
90 days	0.59	0.77

Kaplan-Meier curves and proportion survivors of patients with or without cancer with bloodstream infection caused by any pathogen (upper panels), a Gram-positive micro-organism (middle panels) or a Gram-negative micro-organism (lower panels). Dotted lines represent patients with cancer, solid lines represent patients without cancer.

Table 3: Blood culture isolates

	Cancer		Non-cancer		
	n=765	(%)	n=4,153	(%)	*p*
Gram-positive	**449**	**(58.7)**	**2,551**	**(61.4)**	***0.17***
Staphylococcus aureus	45	(5.9)	345	(8.3)	*0.03*
Coagulase negative Staphylococci[1]	212	(27.7)	1,217	(29.3)	*0.30*
Streptococcus pneumoniae	25	(3.3)	200	(4.8)	*0.07*
Hemolytic Streptococci (A,B,C,F,G)	5	(0.7)	135	(3.3)	*<0.01*
Other *Streptococcus* species[2]	20	(2.6)	169	(4.1)	*0.07*
Enterococcus faecalis	59	(7.7)	196	(4.7)	*<0.01*
Enterococcus faecium	33	(4.3)	82	(2.0)	*<0.01*
Other Enterococcus species[3]	5	(0.7)	28	(0.7)	*0.80*
Other gram-positive organism[4]	45	(5.9)	179	(4.3)	*0.07*
Gram-negative	**243**	**(31.8)**	**1,342**	**(32.3)**	***0.65***
Escherichia coli	100	(13.1)	758	(18.3)	*<0.01*
Pseudomonas aeruginosa	36	(4.7)	91	(2.2)	*<0.01*
Haemophilus (para-)influenzae	1	(0.1)	17	(0.4)	*0.40*
Klebsiella pneumoniae	25	(3.3)	108	(2.6)	*0.40*
Other *Klebsiella* species[5]	15	(2.0)	50	(1.2)	*0.10*
Proteus[6]	7	(0.9)	89	(2.1)	*0.03*
Serratia[7]	11	(1.4)	34	(0.8)	*0.10*
Enterobacter cloacae	19	(2.5)	42	(1.0)	*<0.01*
Other *Enterobacter* species[8]	3	(0.4)	15	(0.4)	*0.80*
Citrobacter[9]	9	(1.2)	26	(0.6)	*0.20*
Fermentative gram-negative rods[10]	10	(1.3)	21	(0.5)	*0.02*
Non- fermentative Gram-negative rods[11]	3	(0.4)	45	(1.1)	*0.10*
Other gram-negative organisms[12]	4	(0.5)	46	(1.1)	*0.20*
Anaerobes[13]	**39**	**(5.1)**	**132**	**(3.2)**	***0.02***
Enteropathogens	**3**	**(0.4)**	**28**	**(0.6)**	***0.60***
Salmonella species[14]	3	(0.4)	26	(0.6)	*0.60*
Other enteropathogens[15]			2	(0)	
Yeast	**23**	**(3.0)**	**63**	**(1.5)**	***0.03***
Candida albicans	10	(1.3)	32	(0.8)	*0.20*
Other *Candida* and yeast species[16]	13	(1.7)	31	(0.7)	*0.02*
Other micro-organism	**5**	**(0.7)**	**11**	**(0.3)**	***0.20***
Missing	**3**	**(0.4)**	**26**	**(0.6)**	***0.60***

[1] *Includes Staphylococcus epidermidis, haemolyticus, hominis, hyicus, lentus, lugdunensis, pasteuri, saprophyticus, schleiferi, simulans, warneri, xylosus, carnosus, cohnii, urealyticum, capitis. Dermacoccus nishinomlyaensis, Micrococcus luteus, Stomatococcus mucilaginosus.*

[2] *Includes Streptococcus mitis, bovis (1&2), sanguis, salivarius, mutans, oralis, parasanguinis, sobrinus, vestibularis, acidominimus, anginosusm, constellatusm, cristatus, dysgalactiae, equisimillis, equinus, gallolyticus.*

[3] *Includes Enterococcus casseliflavus, gallinarum, durans.*

[4] *Includes Difteroid rods, Bacillus cereus, circulans, Corynebacterium accolens, amycolatum, minitissimum, stri-*

atum, jeikeium, propinquum, Leuconostoc species, Propionibacterium acnes, Rothia mucilaginosa, Aerococcus, Lactococcus and unspecified Gram-positive bacteria.

[5] *Includes Klebsiella oxytoca, ozaenae.*

[6] *Includes Proteus mirabilis, vulgaris.*

[7] *Includes Serratia marcescens,liquefaciens, odorifera, plymuthica.*

[8] *Includes Enterobacter aerogenes, sakazakii, hermannii.*

[9] *Includes Citrobacter freundii, koseri, werkmanii, amalonaticus, braakii, farmer.*

[10] *Includes Morganella morganii, Aeromonas caviae, hydrophila, sobria, Eubacterium aerofaciens, Hafnia alvei, Providencia rettgeri,stuartii, Raoultella terrigena.*

[11] *Includes Acinetobacter baumannii, calcoaceticus-baumannii complex, lwoffii, haemolyticus. Alcaligenes faecalis, Chryseobacterium indologenes, meningosepticum, Metylobacterium mesophilicum, Rhizobium radiobacter, Stenotrophomonas maltophilia, Achromobacter xylosoxidans.*

[12] *Includes Neisseria species, Moraxella catarrhalis, Listeria monocytogenes.*

[13] *Includes Bacteroides fragilis,Clostridium paraputrificium, perfringens (welchii), septicum, tertium, Fusobacterium necrophorum, nucleatum, Pasteurella multocida, Bifidobacterium species, Gemella morbillorum, -Peptostreptococcus saccharolyticus, Prevotella loescheii, oralis.*

[14] *Includes Salmonella group B, C, D, paratyphi A, typhi. Typhimurium*

[15] *Shigella sonnei, Campylobacter jejuni.*

[16] *Includes Candida glabrata, intermedia, krusei, parapsilosis, tropicalis, and other types of yeast.*

Table 4: Blood culture isolates in patients with a central venous catheter

	Cancer		Non-cancer		
	n=219	(%)	n=700	(%)	*p*
Gram-positive	**156**	**(71.2)**	**564**	**(80.6)**	***<0.01***
Staphylococcus aureus	8	(3.7)	27	(3.9)	*0.90*
Coagulase negative Staphylococci	91	(41.6)	346	(49.4)	*0.05*
Streptococci	1	(0.5)	7	(1.0)	*0.70*
Enterococci	26	(11.9)	99	(14.1)	*0.50*
Other Gram-positive organisms	30	(13.7)	85	(12.1)	*0.60*
Gram-negative	**48**	**(21.9)**	**98**	**(14.0)**	***<0.01***
Escherichia coli	3	(1.4)	8	(1.1)	*0.90*
Pseudomonas aeruginosa	16	(7.3)	22	(3.1)	*0.01*
Klebsiella	8	(3.7)	12	(1.7)	*0.10*
Proteus	2	(0.9)	7	(1.0)	*0.80*
Serratia	6	(2.7)	8	(1.1)	*0.07*
Enterobacter	3	(1.4)	11	(1.6)	*0.90*
Citrobacter	2	(0.9)	4	(0.6)	*0.90*
Other Gram-negative organisms	8	(3.7)	26	(3.7)	*0.80*
Yeast	**10**	**(4.6)**	**28**	**(4.0)**	***0.90***
Candida albicans	5	(2.3)	17	(2.4)	*0.90*
Other yeast species	5	(2.3)	11	(1.6)	*0.70*
Other micro-organisms	**5**	**(2.3)**	**10**	**(1.4)**	***0.60***

Table 5: Antimicrobial resistance in cultured isolates in patients with cancer and non-cancer patients

	Cancer patients			Non-cancer patients			
	#	Resistant (%)		#	Resistant (%)		*p*
Staphylococcus aureus							
oxacillin	45	0	(0)	345	5	(1.4)	*0.90*
erytromycin	33	3	(9.1)	233	34	(14.6)	*0.60*
vancomycin	37	0	(0)	315	1	(0.03)	*0.20*
Streptococcus pneumoniae							
penicillin	24	0	(0)	190	4	(2.1)	*0.90*
erytromycin	24	2	(8.3)	184	22	(12.0)	*0.90*
Enterococcus faecalis							
ampicillin	55	0	(0)	159	0	(0)	-
vancomycin	55	1	(1.8)	177	4	(2.3)	*0.70*
Enterococcus faecium							
ampicillin	27	19	(70.4)	76	59	(77.6)	*0.60*
vancomycin	27	0	(0)	79	7	(8.9)	*0.20*
Escherichia coli							
ampicillin	95	46		703	302		*0.40*
ciprofloxacin	93	5	(5.4)	707	74	(10.5)	*0.20*
cefuroxim	94	8	(8.5)	692	44	(6.4)	*0.60*
ceftazidime	92	4	(4.3)	699	23	(3.3)	*0.80*
meropenem	63	0	(0)	557	0	(0)	-
Klebsiella pneumoniae							
ampicillin	23	22	(95.7)	103	101	(98.1)	*0.90*
ciprofloxacin	23	1	(4.3)	100	7	(7.0)	*0.90*
cefuroxim	23	2	(8.7)	99	8	(8.1)	*0.70*
ceftazidime	23	2	(8.7)	103	7	(6.8)	*0.90*
meropenem	15	0	(0)	98	0	(0)	-
Pseudomonas aeruginosa							
ciprofloxacin	30	6	(20)	81	5	(6.2)	*0.07*
ceftazidime	25	1	(4)	75	3	(4)	*0.60*
meropenem	24	5	(20.8)	70	0	(0)	*<0.01*

 # Number of samples tested

Survival

To obtain insight into the impact of documented BSI on outcome we determined 30-, 60 and 90-day all-cause mortality following blood culture positivity in both patient groups (Figure 1). Cancer patients with BSI had a significantly increased crude mortality when compared to patients without cancer. Differences between cancer and non-cancer patients were present in both Gram-positive and Gram-negative BSI, albeit to a larger extent in the latter group.

Table 6: Bloodstream infections in neutropenic patients (absolute neutrophil count <1x10^9 per liter)

	Cancer (%) n=9		Non-cancer (%) n=26	
Gram-positive	**4**	**(44.4)**	**16**	**(61.5)**
Staphylococcus aureus			2	(7.7)
Coagulase negative Staphylococci	2	(22.2)	6	(23.1)
Streptococcus pneumoniae			5	(19.2)
Other Streptococci	1	(11.1)	3	(11.4)
Other Gram-positive organism	1	(11.1)		
Gram-negative	**5**	**(55.5)**	**10**	**(38.5)**
Escherichia coli	3	(33.3)	5	(19.2)
Pseudomonas aeruginosa	1	(11.1)	1	(3.8)
Haemophilus (para-) influenzae			2	(7.7)
Proteus mirabilis			1	(3.8)
Other micro-organisms	**1**	**(11.1)**	**1**	**(3.8)**

Discussion

Current knowledge of causative organisms in BSI in patients with cancer is predominantly derived from investigations performed in specialized cancer treatment centres. The primary objective of the current study was to obtain insight into the distribution of pathogens causing BSI in cancer patients (as compared with patient without malignancy) in the setting of a community teaching hospital. For this we analysed all positive blood culture results obtained in our institution from adult patients between January 2005 and January 2011. We found a predominance of Gram-positive isolates in both patients with and patients without cancer. Positive blood cultures in cancer patients were caused more often by enterococci, *P. aeruginosa*, *E. cloacae* and yeasts when compared with non-cancer patients, while patients without malignancy had more positive blood cultures for haemolytic streptococci and *E. coli.* Mortality rates were much higher in patients with cancer. With the exception of meropenem resistance by *P. aeruginosa* no difference in antimicrobial resistance patterns were found between bacteria cultured in cancer and non-cancer patients. The difference in meropenem resistance might be related to local transmission of a *Pseudomonas* strain in the oncology unit as has been described in nosocomial outbreaks [19].

The current cohort of cancer patients with BSI predominantly consisted of patients with solid tumours (85.5%). As such, our result predominantly apply to this group of cancer patients. Previous studies have documented differences in causative BSI pathogens in patients with solid tumours and haematological malignancies, with a higher incidence of *E. coli* and *Klebsiella* spp. in the latter group [20].

Our study comprised all BSI irrespective of place of acquisition or hospital location. We found a marked predominance of Gram-positive organisms in both patients with and without cancer (58.7 and 61.4% respectively). Similarly, in a cohort of 2,340 cancer patients with nos-

ocomial BSI 61% of all episodes were caused by Gram-positive organisms [12]. The most frequently isolated pathogens in our investigation were coagulase negative staphylococci, *E. coli*, *S. aureus* and enterococci, which resembles the data obtained from nosocomial blood cultured isolates in cancer patients in the United States [12]. Similarly, coagulase negative staphylococci, *S. aureus* and *E. coli* were reported as most frequent BSI pathogens in various rank orders in patients with haematological malignancies or solid tumours [15, 21, 22]. The current results in addition show that among these common BSI pathogens, enterococci were more prevalent in cancer patients and *E. coli* in non-cancer patients. *E. faecalis* was more common than *E. faecium* in our study (7.7 and 4.3% of all isolates respectively), whereas in the United States nosocomial BSI were caused more often by *E. faecium* (5.2%) than *E. faecalis* (4.6%) [12]. Cancer has been implicated as a risk factor for BSI by a number of specific pathogens, including *S. aureus* [23], *E. coli* [24], *K. pneumoniae* [25] and *P. aeruginosa* [26]. However, we only found an increased incidence of *P. aeruginosa* in cancer patients, whereas *S. aureus* and *K. pneumoniae* were equally common in both patient groups and *E. coli* was more frequent in patients without cancer. Fungi accounted for 10% of BSI isolates in hospitalized cancer patients in the United States [12] versus only 3% in the current study, which at least partially can be explained by differences in the populations studied (i.e. restricted to nosocomial BSI in the earlier investigation) [12].

In the subgroup of patients in whom neutrophil counts were measured, cancer patients had absolute neutropenia in < 5% of cases versus < 2% of non-cancer patients; this group was too small to adequately investigate the impact of neutropenia on BSI pathogens. Of note, however, in the largest study performed to date neutropenia only modestly influenced the distribution of specific causative organisms of BSI in cancer patients, with a slightly altered incidence of viridans group streptococci (increased) and *E. faecium* (reduced) in neutropenic patients; the incidence of the most common BSI pathogens was not influenced by the presence or absence of neutropenia [12]. Another smaller study conducted in a tertiary oncology care center with a mixed solid tumor and hematological malignancy population reported higher incidences of BSI caused by *E. coli*, *Klebsiella* spp. and *P. aeruginosa* in neutropenic patients [20].

The impact of BSI on outcome was evaluated by determining 30-, 60- and 90-day mortality; we considered assessment of mortality beyond this time point of less relevance because late deaths are less likely to be related to the BSI and more likely to cancer. Nonetheless, the extent to which the cancer itself, more so than the BSI per se, contributed to short-term mortality cannot be deducted from our study. Cancer patients had a 90-day mortality of 35.8% following BSI caused by any pathogen versus 23.5% in patients without cancer. In the largest survey conducted to date, in hospital mortality following nosocomial BSI was 36% for neutropenic patients and 31% for patients without neutropenia [12]. Earlier investigations reported mortality rates of 20-25% of BSI in patients with solid tumours [1, 27, 28]. In accordance with the current results, in ICU patients with documented infection cancer was associated with a greater risk of hospital death [6]. Notably, in cancer patients we found a considerably higher 90-day mortality after Gram-negative BSI (41.4%) than after Gram-positive BSI (31.2%); this difference in 90-day mortality after Gram-negative and Gram-positive BSI was not present in patients without cancer (22.3 and 23.8% respectively).

We evaluated several laboratory results obtained in the period from 24 hours before to 48 hours after blood culture positivity. We specifically chose for this time window in order to obtain insight in the systemic response to BSI in both patient groups. Based on C-reactive pro-

tein levels (inflammatory response), platelet counts and prothrombin time (both indicative of coagulopathy) cancer patients did not differ from non-cancer patients. Patients with malignancy did show lower albumin concentrations, which could have been caused by either a stronger acute phase response (albumin is a negative acute phase protein) or a worse pre-existing nutritional status; the latter explanation may be more likely considering the similar C-reactive protein levels in both patient groups. Cancer patients did not show more evidence of renal insufficiency during BSI; on the contrary, plasma creatinin concentrations were even higher in patients without cancer.

There are some important limitations in this study. First, our survey represents a descriptive retrospective evaluation using laboratory and hospital information systems data; clinical data and bloodstream isolates were not prospectively collected. Second, no information is available regarding the source of infection in patients with bacteremia. We can not exclude that differences exist in the source of infection between cancer and non-cancer patients. Such differences could also influence the likelihood of survival in these patients. Furthermore, positive blood cultures not necessarily imply the presence of blood stream infections but could also result from skin contaminants. In this respect, it is important that coagulase negative staphylococci represented almost 30% of cultured isolates. The clinical significance of these isolates remain unknown. However, as the proportion of coagulase negative staphylococci among bacteria from positive blood cultures was similar we can conclude that the presence of cancer has no important influence on the likelihood of coagulase negative staphylococci as causative microorganism in BSIs. In this study, positive blood cultures with the same bacteria were considered as distinct cultures if taken more than 24 hours apart. Consequently, the number of positive cultures as reported here may be an overestimation of the true incidence. However, this limitation applies equally for both cancer and non-cancer patients. Therefore, we consider it unlikely, that this definition could have an important influence on the comparisons between cancer and non-cancer patients made in this study. Finally, a limitation of our retrospective study is that in only one third of patients peripheral blood neutrophil counts were determined within the time window of 24 hours before to 48 hours after the positive blood culture.

In conclusion, we here report that in a large community teaching hospital in the Netherlands Gram-positive organisms are the most common isolates from blood cultures in both cancer and non-cancer patients. Specific pathogens were more present in cancer patients, in particular enterococci, *P. aeruginosa*, *E. cloacae* and yeasts. Mortality rates after BSI were much higher in cancer patients than in patients without cancer with the greatest difference in BSI caused by Gram-negative bacteria.

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LOW COMPLICATION RATES IN THE USE OF PORT-A-CATHS IN ONCOLOGY PATIENTS

CHAPTER 7

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Abstract

Background: Port-A-Caths (PACs) represent an important component of the care of cancer patients, in particular for administration of chemotherapy. We here sought to analyse the longevity and complications of PACs in cancer patients in a large community hospital.
Methods: We retrospectively analysed the indications, duration of use, complications and reasons for removal of PACs in cancer patients treated in our centre from January 2005 to December 2010, and compared these with findings in patients who received a PAC in the same period for reasons not related to cancer.
Results: During the study period 152 cancer patients received a total of 170 PACs; in the same period, 21 patients received a total of 35 PACs for reasons unrelated to cancer. The total analysis comprised 70.919 days of PAC use. Most cancer patients had a solid tumour (97%). PACs were removed because of a complication in 25 cases in cancer patients (14.7%) versus 15 cases in non-cancer patients (42.9%, $P < 0.01$). Culture proven infection was the reason for PAC removal in 16 cases in cancer patients (23.5%) versus 8 cases in non-cancer patients (42.1%; P =ns). The total number of PAC associated infections was 20 in cancer patients (0.35 infections per 1,000 PAC days) versus 19 in non-cancer patients (1.43 infections per 1,000 PAC days; $P <0.01$). No PAC associated thrombosis was found.
Conclusion: In clinical practice the use of PACs in cancer patients is safe with lower complication rates when compared with PAC use in patients without malignancy.

Introduction

Venous access is problematic for oncology patients receiving repeated courses of cytotoxic therapy. Totally implantable ports connected with a central venous catheter were first introduced in 1982 and soon replaced subcutaneously tunnelled catheters such as Hickman, Groshong and Broviac lines [1, 2]. These totally implantable venous access ports (TIVAPs), among which Port-A-Caths (PACs), now represent an important component of the regular care of cancer patients by providing a simple way of accessing the venous system for administration of chemotherapy, antibiotics, analgesics, blood products and fluids, and for the collection of blood. Although in general these devices are safe, their use can be associated with significant complications, most notably infection and thrombosis.

Previous studies have examined complication rates of PAC use in cancer patients [3-11]. Such knowledge is significant considering the importance of PACs for the clinical care of cancer patients and for guiding preventive measures. This in particular holds true for the main complications described in literature, infection and thrombosis. In the current study we retrospectively analysed the indications, duration of use, complications and reasons for removal of PACs in patients with malignancies treated in our centre (a large community hospital in the Netherlands) from January 2005 to December 2010. In addition, we analysed the microbial causes of PAC associated infections in these patients and their impact on PAC use and removal. In order to obtain insight into complications that may relate to cancer specifically, we compared findings in cancer patients with those in patients who received a PAC in the same period for reasons not related to cancer.

Materials and Methods

Patients

We performed a retrospective analysis of 173 adult patients (> 18 years of age) who received a total of 205 PACs between January 2005 and December 2010 in the Reinier de Graaf Hospital in Delft, the Netherlands. The analysis was approved by the institutional medical ethics committee.

Study design

Porth-A-Cath removals within two days after implantation were excluded since these were considered related to the surgical procedure. A single type of PAC was used (Deltec™, Smiths Medical). The PACs were placed by surgeons from the Department of Vascular Surgery in the operation room under general or local anaesthesia using a standardized surgical technique. The access route was chosen according to the patient's anatomy, preferably the right subclavian or external jugular vein. Prophylactic antibiotics were not routinely administered. The PACs were accessed and cared for by trained nursing staff. Lock with heparin solution was done after every PAC access and every four weeks if the PAC was not in use. Patients did not receive routine anticoagulant therapy. PAC associated infection was defined as (1) a positive culture of blood obtained from either a peripheral vein or from the port and (2) clinical suspicion of PAC infection as reflected by local symptoms or absence of another infectious source [12]. For the analysis of PAC associated infections, multiple positive blood cultures with a single pathogen in one clinical episode were counted as one PAC associated infection with this pathogen [12]. The

occurrence of a PAC associated infection was defined as a complication; other non-infection related complications were analysed by studying reasons for PAC removal making use of patient hospital records. Diagnostic procedures were done as ordered by the physician; systematic venographies were not done. Minor complications such as local pain, skin irritation and/or transient inability to draw blood from the PAC were not analysed.

Statistical analysis

Data are expressed as means, medians, interquartile range and ranges as indicated. Differences between cancer patients and non-cancer patients were analysed by Mann-Whitney U test, Chi square test or Log Rank test. A p value below 0.05 was considered to be statistically significant.

Results

Patients

From January 2005 to December 2010 152 patients with a malignancy received a total of 170 PACs; in the same period, 21 patients received a total of 35 PACs for reasons unrelated to cancer (Table 1). In both groups, more women than men received a PAC (73.7% amongst cancer patients and 61.9% amongst non-cancer patients). The vast majority of patients with a malignancy suffered from a solid tumour, with breast and colorectal cancer as the predominant diagnoses (47.4% and 32.9% respectively). In non-cancer patients neuromuscular disease was the most frequent diagnosis (57.1%). The total analysis comprised 70,919 days of PAC use, of which 57,642 days in cancer patients and 13,277 days in non-cancer patients. In cancer patients all PACs were used for administration of chemotherapy. In 14 cases (9.2%) it was also used for immunotherapy. In non-cancer patients 10 PACs (47.6%) were placed for immunotherapy and 8 PACs (38.1%) for chronic treatment with dopamine for heart failure (table 1).

Longevity of PACs

Table 2 shows the longevity and reasons for removal of the inserted PACs. Twenty percent of PACs in cancer patients were in use at the end of follow-up, compared with 31.4% in non-cancer patients (p=ns). Figure 1 is a Kaplan Meier plot showing that the average survival of the PACs was similar in cancer and non-cancer patients (mean time to removal 927 days vs. 899 days, p=0.9 by log rank test). The percentage of PACs removed during the follow-up period was 40% in cancer patients and 51.5% in non-cancer patients (p=ns). The mean number of days a PAC was in situ at the time of removal was 309 days and 500 days in cancer and non-cancer patients respectively, p=ns). In cancer patients, most PACs were removed because therapy was completed (63.2% vs. 15.8% in non-cancer patients, p<0.01). Twenty-five (14.7%) and 15 (42.9%) of PACs were removed for complications (infectious or non-infectious) in cancer and non-cancer patients respectively (p<0.01).

PAC associated infections

PAC associated blood stream infection occurred in 25 of 173 patients (14.4%) (Table 3). Amongst cancer patients, 18 (11.8%) were diagnosed with PAC associated infection during the study period, versus 7 (33.3%) non-cancer patients (P = 0.02). The total number of PAC associated infections was 21 in cancer patients (0.36 infections per 1,000 PAC days) versus 18 in non-cancer patients (1.4 infections per 1,000 PAC days; P < 0.01 versus cancer patients); Of interest,

Table 1: Patient characteristics and indications for PAC placement

	Total	Cancer patients		Non-cancer patients	
Number of PACs (%)	205	170 (82.9)		35 (17.1)	
Number of patients (%)	173	152 (87.9)		21 (12.1)	
Female (%)	125 (72.3)	112 (73.7)		13 (61.9)	
Male (%)	48 (27.7)	40 (26.3)		8 (38.1)	
Mean age (range) at time of PAC placement	51.8 (18-80)	51.7 (26-77)		53.5 (18-80)	
Diagnosis (%)					
		Breast cancer	72 (47.4)	Neuromuscular disease[1]	12 (57.1)
		Colorectal cancer	50 (32.9)	Congestive heart failure	8 (38.1)
		Upper GI cancer	9 (5.9)	CIVD[2]	1 (4.8)
		Ovarian cancer	11 (7.3)		
		Lymphoma	4 (2.6)		
		Other	6 (3.9)		
Indication					
- Chemotherapy		152 (100)		-	
- Immunotherapy[3]		14 (9.2)		10 (47.6)	
- Analgesics		-		2 (9.5)	
- Dopamine		-		8 (38.1)	
- Biphosponate (APD)		-		1 (4.8)	
Mean (range) number of days in situ					
- Total	70,919	57,642		13,277	
- Per PAC	346 (9 - 2,064)	339 (9 - 2,064)		379 (13 - 1,839)	

[1] Dystrophia (N=4), Chronic inflammatory demyelinating polyneuropathy (N=6) and multiple sclerosis (N=2).
[2] Common variable immunodeficiency.
[3] Refers to monoclonal antibodies: in cancer patients trastuzumb (Herceptin®, antibody directed against epidermal growth factor receptor-2) or bevacizumab (Avastin®, antibody directed against the vascular endothelial growth factor receptor), in non-cancer patients gammaglobuline (Gammagard®).

the median time that a PAC was in situ before a blood stream infection occurred was shorter in cancer patients than in non-cancer patients (100 versus 414 days respectively, P = 0.01). The cumulative proportion of PACs removed for an infectious complication is shown in figure 2. Causative organisms did not differ between cancer and non-cancer patients (Table 3). In both groups, gram-positive pathogens, in particular *Staphylococcus aureus* and coagulase negative staphylococci, were most prevalent (more than two thirds of all blood stream infections).

Discussion

In the last decades, much attention has been given to the achievement of an adequate means of venous access in cancer patients that is suitable for long-term use, in particular for repeated administration of chemotherapy and blood draw for testing. Totally implantable venous access

Table 2: Number and reasons for PAC removal

PACs	Total (n = 205)	Cancer (n = 170)	Non-cancer (n = 35)
Number of PACs in situ at closure of data collection (%)	45 (22.0)	34 (20.0)	11 (31.4)
Number of PACs removed (%)	86 (41.9)	68 (40.0)	18 (51.5)
Number of days in situ[1]			
- Mean	353	312	500
- Median	224	215	247
- Range	6-2,064	6-2,064	24 -1,809
Number of patients with PAC removed	77	64	13
- Female	60	51	9
- Male	17	13	4
Reason for removal (% of total removed)			
- Treatment completed	46 (53.5)	43 (63.2)	3 (15.8)
- PAC infection[2]	24 (27.9)	16 (23.5)	8 (42.1)
- Occlusion[3]	4 (4.7)	2 (3.0)	2 (10.5)
- Malfunction[4]	9 (10.5)	4 (5.9)	5 (26.3)
- Other[5]	3 (3.5)	3 (4.5)	0

[1] p=ns for difference between patients with cancer and non-cancer patients

[2] PAC infection is defined as positive culture from blood obtained from the port or a peripheral vein and clinically suspicion of PAC as defined by symptoms or ruling out other foci.

[3] Defined as inability to infuse fluids into the PAC system, confirmed by administration of radiological contrast fluid into the Port.

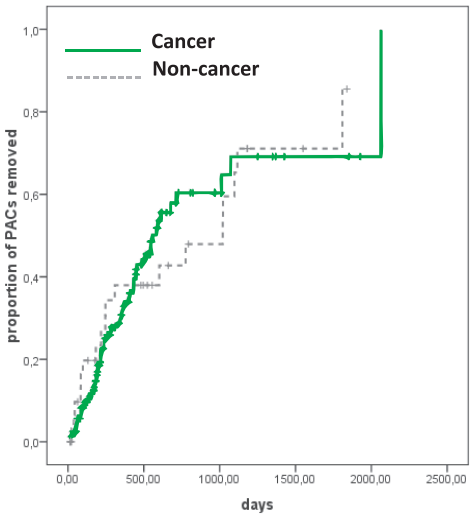
[4] For example nicking of the line, Port moved away into deeper (breast-) tissue, Port turned away.

[5] Due to progressive disease in the chest-wall covering the port, necessity to insert a Levine shunt, fat necrosis around the PAC.

ports, such as PACs are preferred to other approaches for many different reasons, including a reduced risk for infection and thrombosis, less visibility and fewer restrictions on daily activity [13]. We here report on our experience with PACs in a large community hospital in the Netherlands during a six-year period (January 2005 – December 2010), comparing indications, duration of use, complications and reasons for removal in 170 cancer patients and 35 patients without malignancy, comprising more than 70,000 days (which is almost 200 patient years) of PAC use.

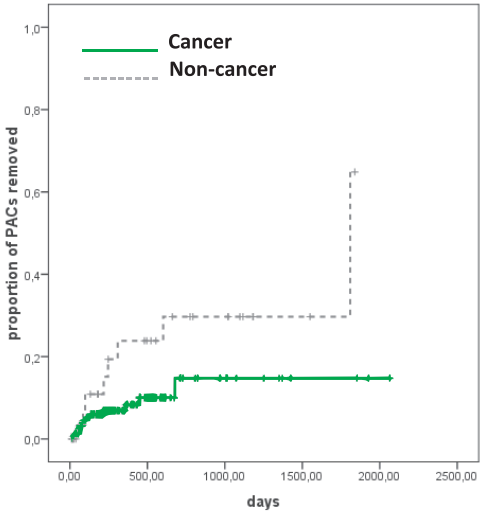
The complication rate of PACs in cancer patients in part depends on the type of malignant disease (solid tumour or haematological malignancy) and neutrophil counts in peripheral blood [13]. In the current analysis the vast majority of oncology patients had solid tumours, in particular breast and colorectal cancer (table 1) and only three patients had leucocytopenia at the time of PAC associated infection (data not shown). Hence, our results predominantly apply to patients with solid tumours and normal leucocyte counts. The current study excluded early complications of PAC placements, such as pneumothorax, primary malposition and arterial

Figure 1: Cumulative proportion of Porth-A-Caths (PACs) removed for any reason



Cases were censored at death or end of follow-up. Cancer patients are in green, non-cancer patients in dotted line. P=ns by log rank test for difference between PACs in patients with cancer and PACs in other patients.

Figure 2: Proportion of Porth-a-Caths (PACs) removed for infectious complications



Cancer patients are in green, non-cancer patients in dotted line. P=0.03 by log rank test for difference between PACs in patients with cancer and PACs in other patients.

Table 3: Porth-a-Caths (PACs) of patients with blood stream infections (BSI) and causative organisms

	All PACs	Cancer	Non-cancer	*p*
Number of PACs inserted	205	170	35	
Number of patients with PAC and BSI (%)	25 (14.4)	18 (11.8)	7 (33.3)	*0.02*
Number PACs with BSI (% of total)	30 (14.6)	18 (10.6)	12 (34.3)	*< 0.01*
Number of episodes of positive blood cultures[1]	39	21	18	*< 0.01*
Number of different organism in these cultures	43	21	22	
Number of days PAC in situ prior to positive blood culture				*0.01*
Median	167	100	414	
IQR	55-553	36-234	125-902	
Causative organisms				
Gram-positive	**29**	**14**	**15**	***ns***
- *Staphylococcus aureus*	10	5	5	
- Coagulase negative staphylococci	16	7	9	
- *Enterococcus*	1	-	1	
- *Streptococcus pneumoniae*	1	1	-	
- Other streptococci	1	1	-	
Gram-negative	**13**	**6**	**7**	***ns***
- *Escherichia coli*	2	1	1	
- *Pseudomonas aeruginosa*	2	-	2	
- *Klebsiella oxytoca*	1	-	1	
- *Klebsiella pneumoniae*	1	1	-	
- *Serratia marcescens*	1	1	-	
- *Rhizobacteria*	1	-	1	
- *Stenotrophomonas maltophilia*	1	-	1	
- *Enterobacter*	2	1	1	
- *Acinetobacter*	1	1	-	
- *Aeromonas hydrophilia*	1	1	-	
Yeasts	**1**	**1**	**-**	**-**
Candida glabratum	1	1	-	

[1] *One blood culture per episode (i.e. if four blood cultures were positive for a particular pathogen during the same infection, only one culture was counted).*

perforation, since these are related to the surgical procedure. The overall rate of removal of PACs for infectious or non-infectious complications was lower in cancer patients compared with non-cancer patients. Furthermore, the risk that a PAC will be removed for infectious reasons is lower in cancer patients than in non-cancer patients. Although a definitive explanation for this difference is lacking, it may be related to a higher experience amongst oncology nurses in the management of PACs and/or differences in underlying diseases. For example insufficient hygienic precautions, inadequate flushing of the system after the introduction of fluids or a too

long interval between usages of the Port make the system at risk for irreversible complications. Insufficient dosing of positive pressure leading to narrowing the lumen of the catheter due to deposits of fibrin or other substances will eventually obstruct the PAC [6]. Different infection rates in cancer and non-cancer patients could have been caused by differences in susceptibility for infection due to the underlying disease. However, although the most important indication for PAC use in non-cancer patients was immunotherapy in the form of infusion of gammaglobulin, this therapy was provided for neuromuscular disease in all but one patient (who had a common variable immunodeficiency). As such, infection rates in non-cancer patients are not biased due to a large number of patients with primary immunodeficiency.

Although PACs are associated with much fewer infectious complications than other approaches to obtain prolonged access to the venous circulation, infection remains an issue of concern [7, 13]. In clinical practice, the diagnosis of PAC associated infection can be made with or without bacteriological confirmation [14, 15]. In the present analysis we only included culture proven infection: PAC associated infection was defined as a positive culture of blood obtained from either a peripheral vein or the port and clinical suspicion of PAC infection as reflected by local symptoms or absence of another infectious source [12]. The incidence of PAC associated infection amongst cancer patients found here (11.8%) is within the same range as that reported in previous studies: positive blood cultures associated with PACs have been reported to occur in 2.4–16.0% of patients [3, 4, 11], representing a major cause of hospital-acquired bacteraemia and the most frequent reason for catheter removal [4, 16]. The vast majority of PAC associated infections were caused by coagulase negative staphylococci and *Staphylococcus aureus*, which is in accordance with earlier investigations [11, 13].

There are no standard criteria for catheter removal in PACs [12, 13]. In the presence of uncomplicated infection due to coagulase-negative staphylococci, the PAC may be retained if there is no evidence of persisting or relapsing bacteraemia. For PAC associated infection caused by pathogens other than coagulase-negative staphylococci, some physicians would retain the port, partially depending on the patient's clinical status. In our analysis, most PAC associated infections resulted in PAC removal in cancer patients (80% of cases), but not in patients without cancer (42%). This difference was not related to a clear difference in causative pathogens. It is conceivable that medical oncologists are reluctant to continue chemotherapy through a PAC that has been infected and that as a consequence thereof PAC associated infection more often leads to PAC removal in cancer patients.

The reported incidence of venous thrombosis as a PAC associated complication varies between zero and 10% [13]. In our centre, thrombosis was never the cause of PAC removal during the six-year study period. Notably, since most cases of catheter-related thrombosis are asymptomatic [13], this does not exclude that thrombosis did occur in our population. Data on prophylactic anti-coagulant therapy are not available for the studied population, but this is not a routine policy in our hospital.

Several earlier investigations examined the complication rate of PACs in a single centre setting. No device related deaths were observed and complications as infection and thrombosis were rare for all type of patients [5, 9, 11] In a Dutch retrospective analysis encompassing a period of 7,5 years (1992 – 1999) involving 38 PACs, the most prevalent complications were infection (two cases or 5.3%) and thrombosis (three cases or 7.9%) [5]. Although the number of PACs studied was relatively low, these data suggest that the incidence of PAC associated thrombosis may have decreased in more recent years, probably at least in part as a result of

better preventive care by the nursing staff.

Our study has several limitations. Firstly, the study has a low sample size relative to the low incidence of PAC related problems, which in particular is true for thrombosis. Secondly, the study groups were not comparable with respect to baseline and prognostic variables, which may hamper appropriate comparisons.

The use of PACs is widely implemented in the clinical care of patients with cancer. These devices have a high acceptance among patients, nurses and doctors. The current analysis illustrates the low rate of complications associated with the use of PACs in the setting of a large community hospital in the Netherlands.

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SUMMARY, GENERAL DISCUSSION & FUTURE PERSPECTIVES

CHAPTER 8

Monique M.E.M. Bos

Summary

The number of patients living with cancer has increased steadily and it has been estimated that close to two-thirds of patients with cancer are long term survivors [1, 2]. This information, paired with the fact that antineoplastic therapies have become more aggressive to accomplish this success, indicates that selective use of critical care for cancer patients not only is reasonable but also necessary. Certainly, the care for acute complications occurring in cancer patients has changed dramatically in recent decades, not only for direct post-operative care following major cancer surgery, but also for cancer patients in need of organ function replacement due to the manifestation of their malignancy or toxicity of the therapies provided. This thesis studies the epidemiology and outcome of critical illness associated with cancer and/or its treatment. Chapters 2-5 describe the proportion of cancer patients that requires admission to an Intensive Care Unit (ICU) during the course of their disease and their characteristics and outcome once in the ICU. Chapters 6 and 7 focus on infectious complications in cancer patients.

Chapter 2 sought to obtain insight into how many cancer patients, stratified according to cancer diagnosis, need ICU care during the course of their disease. This chapter describes a retrospective study in which we collected data from adult cancer patients registered between January 1 2006 and January 1 2011 in four hospitals in four major cities in the Netherlands. Patients were selected based on the hospital patient registration systems containing encoded "Diagnosis Treatment Combinations", a nationwide coding and registration system for all patients entering a hospital, providing information about the type of care, diagnosis and treatment specified by the attending physician [3, 4]. To identify patients from this cohort who were admitted to an ICU during the study period, data were linked with the database of the Dutch National Intensive Care Evaluation (NICE) registry, which contains information on all admissions to the ICUs of 84 hospitals in the country (*i.e.* approximately 90% of all ICUs in the Netherlands) [5]. Of 36,860 patients registered with at least one cancer diagnosis 6.4% was admitted to the ICU during the six-year study period. Surgery was the most common treatment associated with ICU admission: of all cancers treated solely or partially with surgery 11.8% resulted in ICU admission. The fraction of patients that received active treatment with curative intent for a solid tumor was much greater in the ICU group (42.2%) than in the non-ICU group (17.6%). Esophageal cancer most commonly lead to ICU admission (27.3% of patients with this diagnosis); patients with other types of gastrointestinal cancer, including colorectal (10.4%) and pancreatic and biliary cancer (9.4%) also were relatively frequently admitted to the ICU. Although in the general population of cancer patients women (54.0%) were more prevalent than men, the proportion of men that entered the ICU was twice as large when compared with women (9.3 versus 4.0%). Long term survival of cancer patients admitted to the ICU was much lower (median survival time 771 days) than in patients not admitted to the ICU (median survival time not reached). Nonetheless, long-term survival after ICU admission stratified according to cancer diagnosis was substantial.

In Chapters 3 to 5 the NICE registry was further used to study specific subgroups of cancer patients admitted to the ICU: while Chapter 3 focuses on cancer patients with unforeseen ICU admissions, Chapters 4 and 5 zoom in on cancer patients admitted to the ICU after elective and emergency surgery respectively. The objective of **Chapter 3** was to determine the characteristics and outcomes of cancer patients with unplanned admissions to general ICUs, and to compare these with outcomes of unplanned critically ill patients without cancer. For this

we analyzed all unplanned ICU admissions in the Netherlands collected in the NICE registry between January 2007 and January 2011. Of the 140,154 patients with unforeseen ICU admission 10.9% had a malignancy. There appeared to be a strong difference between cancer patients admitted to the ICU for medical or surgical reasons. Medical cancer patients were more severely ill on ICU admission in comparison with medical non-cancer patients, as reflected by higher needs for mechanical ventilation and vasopressors within 24 hours after admission, higher Acute Physiology and Chronic Health Evaluation (APACHE) IV scores and a longer ICU stay (5.1 versus 4.6 days). In contrast, surgical cancer patients only displayed a modestly higher APACHE IV score on admission when compared with non-cancer surgical patients, whereas the other afore mentioned parameters were lower in the surgical cancer patients group. In-hospital mortality was almost twice as high in medical cancer patients as in medical patients without cancer (40.6% versus 23.7%). In-hospital mortality of surgical cancer patients was only slightly higher than in patients without cancer (17.4% versus 14.6%). Hence, the main conclusion of this chapter is that unplanned ICU admission is associated with a high mortality in patients with cancer when admitted for medical reasons, but much less so in cancer patients admitted for surgical reasons. In **Chapter 4** we sought to analyze the characteristics and outcome of patients after ICU admission following elective surgery for different cancer diagnoses. This survey comprised 28,973 elective surgical cancer patients admitted to 80 ICUs in the Netherlands during a five-year period (January 2007 through January 2012); these patients represented 9.0% of all ICU admissions. 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 (CRC, 25.6%), lung cancer (18.5%) and tumors of the central nervous system (14.3%). Overall, ICU length of stay was short (median 0.9 days) with mechanical ventilation (one of four patients) and vasopressor use (one of five patients) as the most prevalent supportive measures. Surgery for esophageal cancer was associated with the longest ICU length of stay (median 2.0 days). 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. This large analysis shows that elective cancer surgery represents a significant part of all ICU admissions, with a short length of stay and low mortality. In **Chapter 5** we focused our attention on emergency surgery, in particular on unplanned ICU admissions after acute surgery for CRC. The aims of this chapter were to compare short-term outcomes of unforeseen ICU admissions after emergency surgery for CRC with those of unplanned ICU admissions after emergency colorectal surgery for non-malignant disease. For this we analyzed all ICU admissions collected in the NICE registry from January 2007 through August 2012. This survey comprised 1,575 CRC patients who received postoperative care in one of 80 participating ICUs after unplanned surgery; these patients were compared with 9,920 patients who received postoperative care after unplanned colorectal surgery for non-malignant disease during the same period in the same ICUs. On ICU admission, CRC patients had a lower prevalence of confirmed infection than patients with non-malignant disease (22.3% versus 41.0%). Patients with CRC had a shorter ICU length of stay than patients without CRC (median 2.3 versus 2.8 days). In addition, CRC patients had a lower ICU mortality (10.3 versus 12.9%). Hospital length of stay and mortality did not differ between groups. In a multivariate analysis in-hospital mortality was associated with high age, low body weight, high severity of illness at ICU admission, chronic comorbidities and metastasized carcinoma. CRC as reason for surgery and gender were not associated with mortality.

The primary objective of **Chapter 6** was to obtain insight into the distribution of pathogens causing blood stream infections (BSIs) in cancer patients (as compared with patient without malignancy) in the setting of a community teaching hospital. For this we analyzed all positive blood culture results obtained in the Reinier de Graaf Hospital in Delft, the Netherlands, from adult patients between January 2005 and January 2011. 4,918 episodes of BSI occurred in 2,891 patients, of whom 13.4% had a diagnosis of cancer. In both cancer and non-cancer patients Gram-positive isolates were more prevalent (58.7 and 61.4% respectively) than Gram-negative isolates (31.8 and 32.3% respectively). Amongst Gram-positive organisms, coagulase negative staphylococci, *Staphylococcus (S.) aureus* and enterococci were most frequently isolated in both patient groups; in cancer patients twice as many BSIs were caused by *Enterococcus (E.) faecalis* and *E. faecium*. Amongst Gram-negative organisms, *Escherichia (E.) coli* was the most common isolate; in cancer patients twice as many BSIs were caused by *Pseudomonas (P.) aeruginosa* and *Enterobacter cloacae*. Yeasts were grown from 3.0% of blood cultures from cancer patients versus 1.5% of cultures from non-cancer patients. Cancer patients had a 90-day mortality of 35.8% following BSI versus 23.5% in patients without cancer; the greatest difference in BSI associated mortality was caused by Gram-negative bacteria. Hence, these findings suggest specific pathogens are more present in cancer patients, in particular enterococci, *P. aeruginosa*, *E. cloacae* and yeasts, and that mortality rates after BSI are much higher in cancer patients than in patients without cancer. In patients with cancer and a central venous catheter, positive blood cultures more often yielded Gram-negative bacteria, in particular *P. aeruginosa*, while coagulase negative staphylococci were more common in non-cancer patients with a central venous catheter. There was no difference in antimicrobial resistance patterns between bacteria cultured in patients with cancer and non-cancer patients

In **Chapter 7** we sought to analyze the longevity and complications of Port-A-Caths (PACs) in cancer patients in the Reinier de Graaf Hospital. We report on the use of PACs in this 600-bed community hospital during a six-year period (January 2005 – December 2010), comparing indications, duration of use, complications and reasons for removal in consecutive patients with and without cancer. During the study period 152 cancer patients received a total of 170 PACs; in the same period, 21 patients received a total of 35 PACs for reasons unrelated to cancer. The total analysis encompassed 82,339 days of PAC use. Most cancer patients had a solid tumor (97%). Fewer PACs were removed because of a complication in cancer patients (14.7%) than in non-cancer patients (42.9%). In addition, the total number of PAC associated infections was lower in cancer patients than in non-cancer patients (0.35 versus 1.43 infections per 1000 PAC days). PAC associated thrombosis did not occur. These results show that in clinical practice the use of PACs in cancer patients is safe with lower complication rates when compared with PAC use in patients without malignancy.

General Discussion

Intensive radiation and chemotherapy together with aggressive surgical techniques have resulted in improved cancer cure rates [1, 2]. This success comes with a price: cancer treatment often is associated with drug- and radiation-related organ toxicities, surgical complications and increased susceptibility to infection [6]. While in the early 1980s the presence of a malignancy was considered a contraindication for admission to an ICU, the success of anti-cancer therapies has created a mind switch amongst clinicians with regard to the use of aggressive and invasive

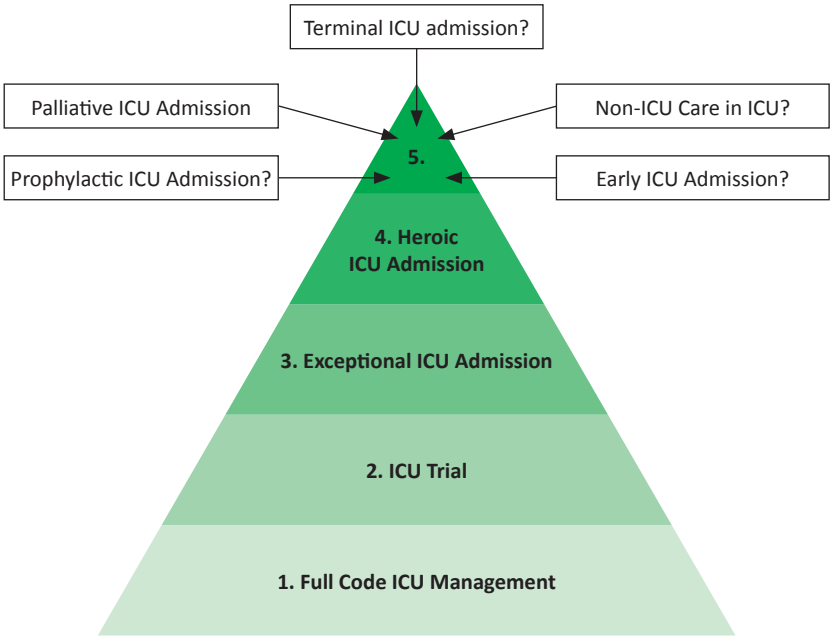
supportive therapy in cancer patients with life threatening conditions due to their disease or treatment [6, 7]. Some investigators even defined ICU admission after 1996 as an independent predictor for a better outcome of cancer patients in the most recent decade [8, 9]. Factors that likely have contributed to improved outcomes include a better patient triage, enhanced management of oncologic emergencies and, in a more general way, advances in critical care management of common ICU conditions such as severe sepsis and acute respiratory distress syndrome.

Indications for ICU admissions in cancer patients

Indications for ICU admission in patients with cancer include postoperative care, complications caused by the malignancy and/or its treatment and crises unrelated to the tumor or its therapy. The most commonly reported reasons for ICU admission of cancer patients are respiratory failure, postanesthetic recovery, infection and sepsis, bleeding and oncologic emergencies [10, 11]. Decisions for ICU admissions of cancer patients with an acute crisis are notoriously difficult. Acute critical illness in patients with a malignancy can have many different clinical presentations and can require a variety of interventions. Early recognition and timely ICU admission may limit or prevent life-threatening cancer-related complications. Current consensus is that the best candidates for use of ICU assets among patients with a malignancy are those with favorable therapeutic options for their cancer and critical illness, or when acute complications occur in patients in whom cancer is in complete remission [7, 12]. Thus, each patient in need for ICU care should be considered in the context of current malignant disease, the presence of comorbidity and capacity to survive the acute clinical event. In case there is not enough information to adequately predict the prognosis of an individual patient reliably, it is reasonable to provide ICU care with reassessment of the patient's condition after several days [12, 13]. A decision not to escalate or stop care may follow if the patient's condition has not improved during this "ICU trial". This strategy is supported by recent data suggesting that duration of mechanical ventilation, use of vasopressors and dialysis are strong predictors of death. For example, patients who require mechanical ventilation for three days or more had a very low survival [14, 15]. Azoulay et l. summarized the ICU admission strategies for cancer patients in a five-step tranche varying from full code curative intent treatment and support to palliative care and support (Figure 1) [6].

While the indications for ICU admission in cancer patients have been fairly well studied, specific knowledge of the percentage of cancer patients from a general population that is admitted to an ICU is highly limited. As such, the study reported in **Chapter 2** is to the first to address this question. The finding that surgery was the most common treatment associated with ICU admission in cancer patients was not unexpected [7, 10, 11]. Notably, in **Chapter 4** we tried to estimate the proportion of cancer patients in the general population that needed ICU admission after elective surgery by comparing data from the Netherlands Cancer Registry, containing all patients with a cancer diagnosis [16], with the data from the NICE registry. The percentages of patients admitted to the ICU stratified according to cancer diagnosis presented in Chapters 2 and 4 show considerable differences, which at least in part can be explained by differences in the cancer populations studied (i.e. all ICU admissions in Chapter 2 versus elective surgical ICU admissions in Chapter 4) and the different methods to estimate these fractions (i.e. by linking DTC of cancer diagnoses in the general population with data in the NICE registry in Chapter 2 versus by approximation using data from the National Cancer Registry and NICE in

Figure 1: Alternative in ICU refusal in cancer patients proposed for ICU admission (reproduced with permission from ref. 6)



	Type of ICU admission	Cinical situation
1.	Full code ICU management	Newly diagnosed malignancy. Malignancy in complete remission.
2.	ICU trial	Clinical response to therapy not available or undetermined.
3.	Exceptional ICU admission	Available effective therapy should be tested in a patient who becomes critically ill.
4.	Heroic ICU admission	Oncologist/hematologist and intensivists agree that ICU admission is not appropiate, but patient or relatives disagree.
5.	Other ICU admissions, not formally evaluated	
	- Prophylactic ICU admission	Earliest phase of high risk malignancies, where admission to the ICU can avoid development of organ dysfunction (tumor-lysis, respiratory failure).
	- Early ICU admission	Admission to the ICU of patients with no organ dysfunction but physiological dysturbances, to prevent late ICU admission (associated with higher mortality).
	- Palliative ICU admission	Admission to the ICU for non-invasive ventilation only.
	- In-ICU non-ICU care	Short ICU admission for optimal and prompt management (catheter withdrawal, early antibiotica etc.).
	- Terminal ICU admission	ICU admission is required to best provide palliative care and symptom control.

Chapter 4). Nonetheless, both analyses revealed esophageal carcinoma, pancreatic-cholangiocarcinoma and CRC as diagnoses that were associated with relatively high ICU admission rates.

Characteristics and outcome of cancer patients in the ICU

Several studies have reported improved in-hospital survival rates of critically ill cancer patients during the past decade [8, 17-22]. The reasons for better survival rates are not totally clear, although several factors may contribute, including a better general ICU care due to improved diagnostic and therapeutic strategies and changes in triage patterns that result in ICU admission of cancer patients with the best chances for survival [6].

Most previous data on the outcome of cancer patients on the ICU are derived from single-center studies conducted in specialized hemato-oncologic ICUs [6]. An important distinction between these earlier investigations and the studies reported in Chapters 2-5 of this thesis lies in the fact that we examined the impact of cancer on the outcome of patients admitted to general ICUs. The analysis reported in **Chapter 3** should be compared with two recent multicenter studies that also investigated the outcome of cancer patients in general ICUs [23, 24]. Important differences between these studies and ours include the number of patients evaluated (> 34,000 versus 473 and 717 cancer patients respectively) and the period during which data were collected (four years versus two weeks and two months respectively) [23, 24]. Chapter 3 and these two previous investigations [23, 24] are in agreement that a cancer diagnosis on admission to a general ICU is far from seldom, varying between 13.5% (Chapter 3), 15.0% [23] and 21.5% [24]. Chapter 3 further shows that amongst unplanned ICU admissions the proportion of cancer patients is lower (9.5%), which possibly is a reflection of the reduced willingness of clinicians to admit cancer patients to the ICU in crisis situations. Moreover, Chapter 3 clearly documents that the outcome of cancer patients in the ICU strongly depends on the admission type. The impact of cancer on mortality especially was large in medical patients, whereas in surgical patients the influence of a cancer diagnosis on mortality was modest at best. In accordance, in a previous study medical cancer patients had a much higher ICU and hospital mortality (44 and 58% respectively) than cancer patients admitted for unplanned surgery (23 and 37% respectively) [24]. Together these data demonstrate that only investigations containing information on the admission type (planned or unplanned, surgical or medical) provide insightful information on the involvement of cancer on ICU and hospital outcome.

The follow up of patients analyzed in Chapter 3 was limited to hospital discharge. This restriction is quite general in current literature and the knowledge of long-term outcome and/or disease-free survival and quality of life after ICU admission of cancer patients is highly limited. The investigations that did study of long-term survival of ICU patients have suggested an increase in mortality during several years after hospital discharge when compared with an age- and gender-matched population [25-27]. In accordance, a very recent study conducted in the Netherlands that analyzed post-ICU mortality up to three years after hospital discharge reported almost two-fold increased mortality rates of cancer patients relative to the total ICU population [28]. **Chapter 2** extends these data, revealing a markedly increased long-term mortality of cancer patients who had been admitted to the ICU relative to cancer patients who were never admitted to the ICU.

Surgical cancer patients in the ICU

ICU physicians are faced with increasing numbers of surgical oncology patients. Surgical pro-

cedures for different malignancies vary substantially, each carrying their own specific risks during acute postoperative care. Many studies have reported on postoperative morbidity and mortality in unselected surgical patient populations [29-33] and many investigations studied postoperative mortality of elective cancer surgery [34-40]. However, only one investigation specifically addressed cancer patients admitted to the ICU after elective surgery; this study, which did not specify the type of surgery, encompassed 381 patients who had a median length of stay on the ICU of two days and an ICU mortality of 6% [24]. As such, the results presented in **Chapter 4**, providing information about the outcome of ICU admission after elective cancer surgery in almost 29,000 patients, are unique in its kind. Hospital mortality stratified according to different types of cancer surgeries was in the same range as reported previously for patients subjected to elective surgery for cancer of the lung [41], esophagus [42, 43], pancreas [44], female genital tract [45], bladder [46] and head and neck [47, 48]. Chapter 4 also shows that approximately one-quarter of elective surgical patients entered the ICU after surgery for CRC. Remarkably, in approximately one third of these patients ICU admission was not foreseen before surgery. In **Chapter 5** we further focused on CRC patients, evaluating the outcome of emergency colorectal surgery in this group. We considered this of interest in light of previously published data showing that one in four cases of bowel cancer are diagnosed only after emergency admission to the hospital [49] and that emergency surgery is as an important risk factor for mortality amongst CRC patients [50, 51]. The high ICU and hospital mortality after ICU admission for acute CRC surgery reported in Chapter 5 (10 and 22% respectively) is in accordance with these earlier studies [50, 51]. Notably, the risk of hospital mortality was not higher in patients with cancer as compared with patients with non-cancer reasons for colorectal surgery requiring ICU admission, and ICU mortality was even lower in patients with CRC. Importantly, our data involve a selected population and do not provide information on in-hospital outcomes of cancer patients who were not admitted to the ICU postoperatively. The decision to admit patients to the ICU is subjective and major differences in the indications for post-operative ICU care after cancer surgery may exist between different hospitals. As such, our results should be interpreted in this context.

Infections in patients with cancer

Infections are a major reason of lengthy hospitalization in patients with cancer [52]. Cancer is associated with a strongly increased risk to acquire BSIs [53-55] and BSIs are a major cause of mortality in patients with a malignancy [56-58]. Many different organisms have been isolated from cancer patients with documented infections, revealing that, besides common pathogens, microorganisms with low virulence can cause significant morbidity and mortality In patients with cancer [59, 60]. Several chapters in this thesis report on infections in cancer patients. **Chapter 3** shows that approximately one third of all medical cancer patients with unplanned ICU admission have a documented infection, which is considerably more than medical patients without cancer. **Chapter 5** documents that one out of ten patients admitted to the ICU after emergency CRC surgery have sepsis. The results presented in **Chapter 6**, showing a predominance of Gram-positive organisms in BSIs in both patients with and without cancer, are in accordance with earlier studies [61-64]. We could not confirm previous investigations that exposed cancer as a risk factor for BSIs by specific pathogens, including *S. aureus* [65], *E. coli* [66] and *K. pneumoniae* [67]. We did find an association between cancer and *P. aeruginosa*, however, which was reported in another study [68]. Clearly, causative pathogens can differ from cen-

ter to center, depending on patient populations (*e.g.* general versus specialized cancer centers and solid versus hematological malignancy) and susceptibility to common antimicrobial agents in the community and hospital.

In **Chapter 7** we addressed a specific risk factor for infections in cancer patients: the use of central vascular catheters, in particular PACs. PACs provide a simple way of accessing the venous system, especially for administration of chemotherapy. Remarkably, the risk for PAC removal for infectious reasons was lower in cancer patients than in non-cancer patients, which is unexpected considering the enhanced susceptibility of cancer patients to infection in general. Conceivably, the fact that oncology nurses likely have more experience than less specialized health care personnel in the management of PACs and/or differences in underlying diseases may contribute to this finding. The incidence of PAC associated infection amongst cancer patients (11.8%) was within the same range as that reported in previous studies [69-71]. In addition, causative pathogens (mainly coagulase negative staphylococci and *S. aureus*) were similar to those reported by others [71, 72].

Impact of gender

Gender may impact on the occurrence of complications and the type of therapeutic interventions while on the ICU. Although overall ICU mortality does not seem to differ between sexes [73, 74], men are more likely to develop sepsis [74-76]. Additionally, men are more likely to receive invasive therapeutic procedures while on the ICU [73, 77]. In this thesis, we examined the influence of gender on several outcome parameters in cancer patients. **Chapter 2** reports that more male than female cancer patients were admitted the ICU in spite of fact that in the general population of cancer patients women were more prevalent than men. While for the overall population this gender difference can be partly explained by the high prevalence of breast cancer (which very rarely results in ICU admission), men more often entered the ICU across all cancer diagnoses with the sole exception of esophageal cancer. This finding is not unprecedented: previous studies pointed out that in general men are more likely to receive ICU care than women [73, 77-79]. At present, it is unclear which factors are responsible for this discrepancy, and further studies are warranted to examine this issue. In **Chapter 5** we hypothesized, based on earlier studies [80-83], that gender could have an important influence on outcome after emergency CRC surgery. However, although in non-cancer emergency colorectal surgery patients admitted to the ICU mortality and in-hospital mortality were higher in female patients, this gender influence was not present in acute CRC surgery even not when adjusted for other covariates.

Future Perspectives

Although knowledge of the characteristics and outcome of cancer patients in the ICU has increased substantially over the past years, most studies on this topic are retrospective and many involve a very heterogeneous patient case mix with medical and surgical patients, solid and hematologic cancer patients, and allogeneic and autologous bone marrow transplant recipients. Results between studies are often difficult to compare because of variations in criteria for ICU admission and discharge, and for end-of-life decisions. As such, many questions remain with regard to care of critically ill cancer patients and future studies are warranted to answer these. Perhaps most importantly, there are very few studies that assessed long-term outcomes

of cancer patients who survive their ICU stay. It is crucial to establish whether ICU or hospital survival results in a real increase in survival with an acceptable quality of life. Hence, more investigations are needed that evaluate outcomes of cancer patients with regard to physical and mental health and quality of life one or several years after ICU admission. Along the same lines, it needs to be established whether cancer patients who survive the ICU are able to receive full chemotherapy regimens and/or other antineoplastic therapies.

In addition, further investigations are necessary to identify predictors of death in cancer patients admitted to the ICU. Factors historically considered to be of crucial importance for outcome of cancer patients on the ICU may no longer be valid. For example, whereas one study reported that the "classic" risk factor neutropenia indeed was associated with a higher mortality in patients with a hematologic malignancy admitted to the ICU [84], a subsequent study from the same institution found no such association [85]. In accordance, a large multicenter study conducted in Brazil failed to find an association between neutropenia and mortality in patients with cancer [24]. Along the same lines, the prognostic importance of other presumptive mortality predictors, such as age or type of the malignancy, is not consistent among different studies and may at least in part depend on ICU admission criteria [6]. Moreover, ICU admission is strongly influenced by the development of less invasive treatment options, associated with less postoperative morbidity such as the implementation of endoscopic esophageal resection versus the traditional transthoracic esophageal resection [86].

Likewise, there is an urgent need for adequate emergency ICU admission criteria for cancer patients. For optimal care of critically ill cancer patients, finding a balance between noninvasive treatments and avoiding delays in optimal therapies are crucial. Current triage criteria for ICU admission are less trustworthy. Indeed, a prospective investigation that examined the outcomes of cancer patients suggested for ICU admission, revealed that 20% of patients who were not admitted because they were considered not sick enough died before hospital discharge (mostly following postponed ICU admission), while 25% of the patients not admitted because they were considered too ill survived [87]. Delayed ICU admission of cancer patients with multiple organ failure is associated with a grim prognosis, and the type and number of organ dysfunctions at ICU admission are good predictors of mortality [15, 21]. Although early ICU admission may improve survival [18], this issue needs proper evaluation, for example by randomizing patients with cancer for ICU admission (or not) in an early phase of their disease or treatment, with only one organ dysfunction. Important for triage, a high functional performance before critical illness has been found to positively influence outcome [88]. Nonetheless, it remains to be established whether performance status scoring systems such as the Karnofsky Performance Scale Index, can assist in identifying patients who will either do well or poorly after ICU admission. Categorizing patients with no improvement or with worsening condition after three days of ICU care, the afore mentioned "ICU trial", may be effective to judge prognoses [12, 15]. However, further studies are warranted to establish the optimal time period for this "therapeutic trial" on the ICU. Once a decision for a "ICU trial" has been made, it is difficult to determine the adequate moment for end-of-life decisions [89]. The switch from curative to palliative care is demanding in cancer patients, not in the least in the setting of an ICU, and the quality of dying must be considered. In this context it should be clear that all patients with cancer admitted to a hospital need to be informed on the existence (or not) of treatment possibilities when acute worsening of their condition is in sight. Discussing the option of a do-not-resuscitate status, whether or not in the presence of relatives, is of great importance.

In case of clinical deterioration, the medical emergency team of that hospital should be aware of the vulnerable status of the patient with a malignant disease and not wait too long before transport to the ICU. A clear protocol on this will increase the efficiency for these patients and the different care-givers involved. When a patient with cancer is admitted to the ICU, daily follow-up (participating in the daily rounds) by the oncologist or hematologist is of great importance to inform the intensive care staff on specific issues regarding the underlying diseases and treatments in the past and future. In situations when a cancer patient can stay in the oncology unit, the medical and nursing staff should be aware of the critical condition of this patient. Meticulous evaluation in a two or three times daily schedule with appreciation of the different organ systems and vital signs should be included in such a routine. It is of great importance that the attending physicians fulfill these responsibilities themselves, teaching the house-staff/ fellows and accentuating that acute deterioration of the patient can result in admission to the ICU.

An aspect not discussed in this thesis are important dilemmas of whether ICU care can be provided simultaneously with cancer-specific treatments, including chemotherapy. Previous studies that addressed this issue have provided evidence that the administration of chemotherapy in the ICU is feasible, with satisfactory short- and long-term results [90, 91]. Moreover, these studies demonstrated patients presenting with severe sepsis or septic shock after recent chemotherapy, may do better that patients who did not receive recent chemotherapy [90, 91]. Although NICE contains information about all patients admitted to the majority of Dutch ICUs, specific information on the complication rate and/or success of chemotherapy in the ICU is not available, and unfortunately very difficult to obtain due to the fact that the NICE database and information of the hospital pharmacist are not linked. Since most cancer patients are treated with multi-modality approaches with curative intent, this information (and long-term follow-up) is of great interest to oncologists and hematologists.

To conclude, the survival rate of cancer patients who require ICU admission has improved due to advances in hematology, oncology and ICU management. The management of critically ill cancer patients requires specialized skills by the intensivist and close collaboration between the intensivist and (hemato-)oncologist. Very likely, at least part of the improvement in the outcome of critically ill cancer patients is the result of tight interactions between intensivists, cancer surgeons and (hemato-)oncologists. Most importantly, (hemato-)oncologists should inform intensivists about curative possibilities for the underlying malignancy. ICU clinicians are more experienced in setting aims of critical care based on the presence of (multiple) organ failure and the potential of reversibility thereof. ICU admission decisions should be made by both specialties based on the acute condition, the prognosis of the malignancy and (obviously) the will of the patient. Decisions to withhold or withdraw life-sustaining therapies are best undertaken by both parties. Information given to patients' relatives and shared decision-making should be presented by both parties together. As such, a close collaboration between intensivists and oncologists is needed to increase the expertise required for all aspects of the general management of cancer patients and to provide optimal care to this population.

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NEDERLANDSE SAMENVATTING, DISCUSSIE EN AANDACHTSPUNTEN VOOR DE TOEKOMST

CHAPTER 9

Monique M.E.M. Bos

Samenvatting

De overleving van patiënten met kanker neemt vooral in ontwikkelde landen sterk toe, waarbij geschat wordt dat ongeveer twee derde van deze patiënten zeer lang leeft met of na de diagnose kanker [1, 2]. Verbetering van de therapeutische opties en de ontwikkeling van een agressievere en veelal multidisciplinaire aanpak van in opzet curatieve behandelingen liggen hieraan ten grondslag. De noodzaak van intensieve zorg voor deze populatie spreekt voor zich. Anticiperen op en behandeling van acute complicaties van anti-kanker therapie zijn in de laatste decaden veranderd en vooral geïntensiveerd. Dit betreft niet alleen de direct postoperatieve zorg van de grote oncologische chirurgie, maar ook het gebruik van orgaan-ondersteunende en vervangende maatregelen noodzakelijk bij uitgebreide infiltratie van een maligniteit in longen, nier of lever. Ook de directe toxiciteit van de lokale en systemische therapie kan hieraan debet zijn. Dit proefschrift betreft meerdere studies en analyses van de epidemiologie en effecten van intensive care (IC) opnamen en behandelingen geassocieerd met een maligniteit en de therapie hiervoor. Hoofdstuk 2-5 beschrijven elk een specifieke groep kankerpatiënten opgenomen op de IC ten tijde van hun ziekte. In hoofdstuk 6 en 7 worden infectieuze complicaties van kanker en antikankerbehandelingen bestudeerd.

In **Hoofdstuk 2** bespreken we een kwantitatieve analyse van het opname patroon van kankerpatiënten op de IC, gestratificeerd naar type maligniteit. Het is een retrospectief onderzoek van volwassen kankerpatiënten over een periode van 5 jaar (januari 2006 tot januari 2011). De database werd samengesteld vanuit een viertal grote ziekenhuizen in de Randstad. Inclusie van patiënten was gebaseerd op de primaire kankerdiagnose opgenomen in de ziekenhuisregistratie middels de Diagnose Behandel Combinatie (DBC). Sinds 2004 zijn in Nederland DBCs geïntroduceerd teneinde gelijkwaardige informatie te verkrijgen van alle patiënten behandeld in de ziekenhuizen met betrekking tot diagnose, type en aard van de behandeling, zoals gespecificeerd door de medische staf [3, 4]. Vervolgens werd dit cohort gekoppeld aan de database van de Nederlandse Intensive Care Evaluatie (NICE) zodat patiënten met kanker en opgenomen op de IC in deze periode, vergeleken konden worden met patiënten uit hetzelfde cohort die niet opgenomen werden op de IC. NICE beschikt over een uitgebreide set gegevens van alle IC opnames van 84 ziekenhuizen in Nederland (ongeveer 90% van alle IC's in Nederland) [5]. Uiteindelijk werden 36,860 patiënten met tenminste één kankerdiagnose in de data base opgenomen. Van hen werd 6.4% opgenomen op de IC gedurende de 5 jaar durende evaluatie-periode. Chirurgie, al of niet gecombineerd met chemotherapie of bestraling, was de meest frequente behandelingsmodaliteit geassocieerd met IC opname (11.8% van alle patiënten die deze behandeling onderging). De fractie van patiënten die een curatieve behandeling onderging was hoger voor de groep die werd opgenomen op de IC dan voor de groep die niet opgenomen werd op de IC (42.2% versus 17.6%). De diagnose slokdarmkanker leidde het vaakst tot IC opname (27.3% van de totale groep met deze diagnose). Ook de andere gastro-intestinale maligniteiten zoals colorectaal carcinoom (CRC)(10.4%) en alvleesklier/galwegkanker (9.4%) waren frequent geassocieerd met IC opname. Hoewel in het hele cohort was het aantal vrouwen (54.0%) groter dan het aantal mannen, werden mannen meer dan twee maal zo frequent opgenomen op de IC (9.3% versus 4.0%). De overleving van kankerpatiënten opgenomen op de IC was significant lager (mediane overleving 771 dagen) dan die van de patiënten niet opgenomen op de IC (mediane overleving nog niet bereikt na 6 jaar) en uiteraard sterk afhankelijk van het type maligniteit. Desalniettemin was de lange termijn overleving van pati-

enten met verschillend type kanker substantieel na IC opname.

Ook voor hoofdstuk 3 tot 5 werd de NICE database gebruikt om de verschillende subgroepen van kankerpatiënten opgenomen op een Nederlandse IC verder te bestuderen: Hoofdstuk 3 betreft de analyse van kankerpatiënten die ongepland op de IC werden opgenomen. In hoofdstuk 4 en 5 beschrijven we de verschillende type chirurgische kankerpatiënten die of electief of na een spoed chirurgische ingreep op de IC werden opgenomen. Het doel van het onderzoek weergegeven in **Hoofdstuk 3** was een directe vergelijking van karakteristieken en mortaliteit tussen kankerpatiënten en patiënten zonder kanker op een IC na een ongeplande opname. Hiervoor werden alle ongeplande IC opnames in Nederland uit de NICE-database geregistreerd in de periode van januari 2007 tot januari 2011 gebruikt. Van de 140,154 acuut opgenomen patiënten had 10.9% kanker. Er was een groot verschil tussen de ongeplande chirurgische kankerpatiënten en de patiënten die om ongeplande medische reden werden opgenomen. Medische kankerpatiënten hadden bij opname een hogere morbiditeit; er was vaker een noodzaak tot mechanische beademing en gebruik van vasopressoren in de eerste 24 uur van de IC opname; deze groep had hogere Acute Physiology and Chronic Health Evaluation (APACHE) IV scores en verbleef langer op de IC (5.1 versus 4.6 dagen) in vergelijking met de ongeplande niet oncologische populatie. De ongeplande chirurgische kankerpatiënten hadden een beperkt verhoogde APACHE IV score bij opname op de IC en minder noodzaak tot beademen en gebruik van vasopressoren. De ziekenhuissterfte van medische kankerpatiënten was bijna twee maal zo hoog dan die van medische niet-oncologische patiënten die ongepland op de IC werden opgenomen (40.6% versus 23.7%). Dit was in veel mindere mate het geval voor chirurgische kankerpatiënten versus niet kankerpatiënten (17.4% versus 14.6%). De uiteindelijke conclusie van het hoofdstuk is dat ongeplande IC opname van kankerpatiënten een hogere morbiditeit en mortaliteit hebben en dat dit vooral geldt voor de groep opgenomen om medische redenen.

Hoofdstuk 4 betreft een studie naar karakteristieken, morbiditeit en mortaliteit van patiënten die opgenomen werden op de IC na het ondergaan van electieve oncologische chirurgie voor verschillende typen van kanker. Dit onderzoek omvatte 28,973 electieve chirurgische kankerpatiënten opgenomen op één van de 80 IC's aangesloten bij NICE gedurende een periode van vijf jaar (januari 2007 tot januari 2012). Deze groep vertegenwoordigde 9.0% van alle IC opnames in deze periode. Hiervan werd 77% gepland opgenomen, terwijl bij 23% tot postoperatieve IC opname besloten werd tijdens of direct na de chirurgische procedure. De meest frequente diagnosen waren CRC (25.6%), long kanker (18.5%) en tumoren van het centrale zenuwstelsel (14.3%). De mediane opnameduur voor alle patiënten tezamen was met 0.9 dagen, kort. Mechanische beademing (één op vier patiënten) en ondersteuning met vasopressoren (één op vijf patiënten) werden het meest frequent toegepast als ondersteunende therapie. Chirurgie voor slokdarmkanker was geassocieerd met de langste IC opnameduur (mediaan 2.0 dagen). De mortaliteit was laag, namelijk 1.4% op de IC en 4.7% in het ziekenhuis. De ziekenhuissterfte nam geleidelijk af in de opeenvolgende jaren van de analyse: van 5.7% in 2007 naar 4.1% in 2011. De uiteindelijke conclusie van te hoofdstuk is dat electieve oncologische chirurgie een significant deel van alle IC opnames betreft met een korte opnameduur en lage mortaliteit. In **Hoofdstuk 5** wordt vervolgens een andere oncologisch chirurgische populatie bestudeerd, namelijk patiënten met CRC die ongepland opgenomen werden op de IC na een spoedoperatie. Twee patiënt groepen werden vergeleken: de geselecteerde patiënten die acuut opgenomen werden op de IC na spoed chirurgie voor CRC en patiënten met een ongeplande IC opname na colorectale spoedchirurgie vanwege een niet oncologische reden.

Gegevens werden verkregen uit de NICE database in de periode januari 2007 tot augustus 2012. Uiteindelijk voldeden 1,575 patiënten met CRC en 9,920 niet-oncologische patiënten aan deze criteria. Patiënten opgenomen op de IC na chirurgie voor CRC hadden minder infectieuze complicaties (22.3% versus 41.0%) en een korter verblijf op de IC (mediaan 2.3 versus 2.8 dagen). Tevens was de IC sterfte voor patiënten na spoedchirurgie voor CRC lager (10.3% versus 12.9%). Ziekenhuis sterfte en verblijfsduur verschilden niet tussen beide groepen. In de multivariaat analyse bleek dat ziekenhuissterfte geassocieerd was met hoge leeftijd (>70 jaar), laag lichaamsgewicht, hoge APACHE IV score, chronische co-morbiditeit en gemetastaseerde maligniteit. Chirurgie voor CRC en geslacht waren niet geassocieerd met sterfte. De uiteindelijke conclusie van het onderzoek is dat spoedchirurgie voor CRC geen reden is om patiënten niet op de IC op te nemen.

Het doel van het onderzoek beschreven in **Hoofdstuk 6** was het vergelijken van pathogenen gevonden in bloedkweken bij kankerpatiënten en patiënten zonder een maligniteit, in een perifeer ziekenhuis in Nederland. Alle positieve bloedkweken van volwassen patiënten in de periode van januari 2005 tot januari 2011, verkregen in het Reinier de Graaf Gasthuis te Delft, werden hiervoor gebruikt. In totaal werden 4,918 positieve bloedkweken bij 2,891 patiënten vastgesteld. Van hen had 13.4% een maligniteit. Zowel bij de kankerpatiënten als bij de niet kankerpatiënten kwamen Gram-positieve bacteriën frequenter voor (58.7 en 61.4%) dan Gram-negatieve micro-organismen (respectievelijk 31.8% en 32.3%). Gram-positieve organismen betrof in beide groepen vooral coagulase negatieve stafylococcen, *Staphylococcus (S.) aureus* en enterococcen. Kanker patiënten hadden twee maal zo vaak een positieve bloedkweek met *Enterococcus (E.) faecalis* en *E. faecium*. Van de Gram-negatieve organisme was *Escherichia (E.) coli de* meest frequente verwekker in beide groepen. *Pseudomonas (P.) aeruginosa* and *Enterobacter cloacae* werden twee keer zo vaak gekweekt in kankerpatiënten. Van de positieve bloedkweken van kankerpatiënten betrof 3.0% schimmels, tegen 1.5% van bloedkweken bij niet kanker patiënten. De 90 dagen mortaliteit na een positieve bloedkweek van kankerpatiënten was hoger dan die van de niet oncologische populatie (respectievelijk 35.8% en 23.5%); het grootste verschil in mortaliteit was aanwezig bij Gram-negatieve bacteriëmie. Deze data suggereren dat specifieke micro-organismen frequenter gevonden worden bij patiënten met kanker (zoals enterococci, *P. aeruginosa*, *E. cloacae* en schimmels) en dat de mortaliteit na een positieve bloedkweek veel hoger is voor patiënten met dan voor patiënten zonder een maligniteit. Kankerpatiënten met een centraal veneuze katheter hadden vaker Gram-negatieve bacteriën in de bloedkweek, en dit betrof vooral *P. aeruginosa*. Coagulase negatieve stafylococcen werden frequenter gevonden in bloedkweken van niet kanker patiënten met een centraal veneuze lijn. Er is nagenoeg geen verschil in antimicrobiële resistentie tussen de bacteriën gekweekt bij kanker en niet kanker patiënten.

In **Hoofdstuk 7** beschrijven we een studie naar de klinische meerwaarde en complicaties van geïnstalleerde Port-A-Caths (PACs) bij kankerpatiënten in het Reinier de Graaf Gasthuis. We rapporteren data verzameld over een periode van 6 jaar (januari 2005 – december 2010) in dit ziekenhuis. We vergeleken indicaties, gebruiksduur en complicatie-aard en frequentie tussen patiënten met en zonder kanker bij wie een PAC geïnstalleerd werd. In de studieperiode werden bij 152 kankerpatiënten 170 PACs ingebracht, en bij 21 niet kankerpatiënten 35 PACs. Dit betekende in totaal 82,339 dagen PAC gebruik. De meerderheid van de kankerpatiënten had een solide tumor (97%). Verwijdering van de PAC om reden van complicaties geschiedde vaker in de groep van de niet oncologische patiënten (42.9% versus 14.7%), en ook het aantal

PAC geassocieerde infecties was lager in de patiënten met kanker dan in de groep zonder een maligniteit (0.35 versus 1.43 infecties per 1000 PAC dagen). In de bestudeerde groep werd geen PAC geassocieerde trombose aangetroffen. De uiteindelijke conclusie van het onderzoek luidt dan ook dat PAC gebruik in kankerpatiënten veilig is en gepaard gaat met weinig complicaties, wanneer vergeleken met PAC gebruik bij patiënten zonder kwaadaardige ziekte.

Discussie

Intensieve behandelingen voor maligne ziekten met bestraling, chemotherapie en agressieve chirurgie hebben geleid tot een toename van de curatiekans [1, 2]. Dit succes heeft een prijs: intensieve anti-kanker therapieën zijn geassocieerd met kans op orgaanschade door de cytostatica, bestralingen, chirurgische complicaties en een verhoogde gevoeligheid voor infecties [6]. Enkele decennia geleden werd de diagnose kanker nog als een contra-indicatie voor opname op een IC gezien. Maar als gevolg van de effectievere behandelingen voor vele maligniteiten is de houding van clinici, waaronder intensivisten betrokken bij de intensieve zorg en ondersteuning van deze populatie veranderd [6, 7]. Na 1996 wordt door enkele onderzoekers een IC-opname als onafhankelijke parameter voor betere uitkomst van kankerpatiënten beoordeeld [8, 9]. Factoren die bijdragen aan deze verandering op de IC zijn een betere en adequate triage voor overplaatsing, verbetering van herkenbaarheid en infrastructuur voor oncologische complicaties en uiteraard een verdere verbetering van de IC geneeskunde en management van bijvoorbeeld sepsis en acute longschade.

Indicaties voor IC opname van kankerpatiënten

Redenen voor IC opname van kankerpatiënten betreffen complicaties veroorzaakt door de maligniteit zelf, postoperatieve zorg, andere complicaties als gevolg van de antikanker therapie en noodzaak van intensieve zorg niet gerelateerd aan de kanker (behandeling). De meest voorkomende redenen van opname zijn postoperatieve zorg, respiratoire insufficiëntie, infectie en sepsis, bloedingen en direct oncologische spoedsituaties [10, 11]. Beslissingen betreffende IC opname van acuut zieke patiënten met een maligniteit blijken complex. Acute verslechtering van patiënten met kanker kan zich op verschillende wijzen manifesteren met als gevolg een veelheid aan mogelijke interventies. Vroege herkenning en overplaatsing naar de IC kan levensbedreigende kanker gerelateerde complicaties minimaliseren. De huidige consensus is dat de beste kandidaten voor IC opname die kankerpatiënten zijn die goede therapeutische opties hebben voor de oncologische aandoening en het ontstane klinisch beeld, en uiteraard die patiënten bij wie de maligniteit in een (langdurige) remissie is geraakt [7, 12]. Dat betekent dat voor elke kankerpatiënt bij wie een IC opname overwogen wordt de afweging gemaakt moeten worden tussen de prognose en behandelmogelijkheden van de onderliggende maligniteit, de mate van comorbiditeit en de therapeutische ruimte voor interventie in de acute klinische verslechtering. Wanneer er onvoldoende informatie is om de prognose van een patiënt voor IC opname te voorspellen is het redelijk een korte periode van intensieve zorg op de IC aan te bieden met afspraken voor een herbeoordeling na enkele dagen [12, 13]. Indien er gedurende deze “ICU-trial” geen verbetering is opgetreden kan dan in tweede instantie besloten worden de IC zorg te beëindigen. Deze strategie wordt ondersteund door recente publicaties waarin de duur van mechanische beademing (> 3 dagen), langdurige noodzaak van vasopressoren en dialyse een negatieve impact hebben op de overleving van patiënt [14, 15]. Figuur 1 beschrijft

in vijf stappen een strategie voor IC opname voor oncologische patiënten volgens Azoulay et al. De basis betreft de kankerpatiënt met een goede prognose en conditie die optimaal behandeld dient te worden op de IC. Vervolgens zal elke andere klinische conditie van patiënten weer tot een volgend alternatief leiden, en dus tot nieuwe overwegingen tijdens de IC opname (Figuur 1) [6].

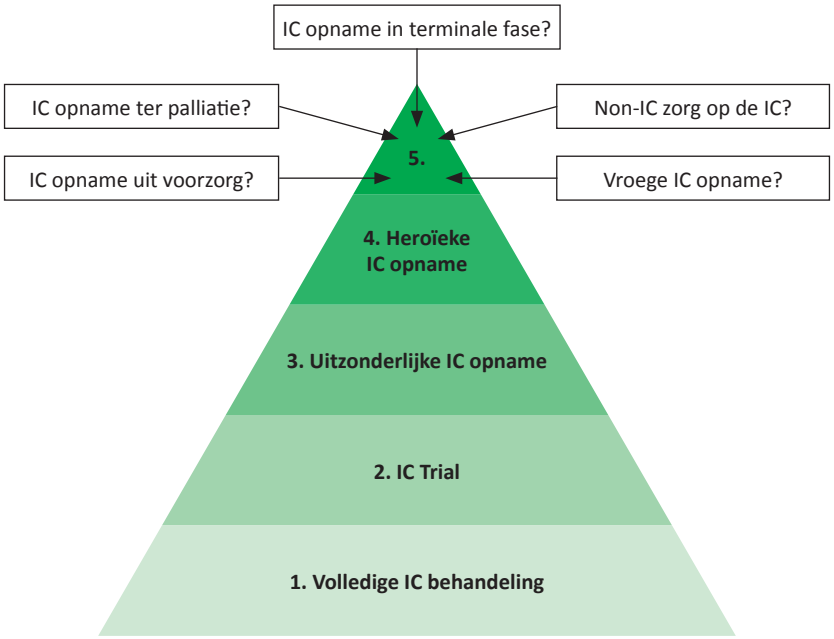
Terwijl de indicaties voor opname op een IC voor kankerpatiënten redelijk goed bestudeerd zijn, is de kennis over het relatieve aantal IC opnames van een algemene oncologische populatie beperkt. In Hoofdstuk 2 wordt deze vraag verder uitgewerkt en geanalyseerd. De eerste conclusie dat chirurgie het meest frequent leidt tot IC opname is op zich niet verrassend [7, 10, 11]. Ook in **Hoofdstuk 4** hebben we op basis van de data uit NICE en de gegevens van de Nederlandse Kankerregistratie een schatting gedaan naar de fractie van patiënten die na een oncologische operatie op de IC worden opgenomen in verhouding met de totale groep kankerpatiënten die een oncologische operatie ondergaan [16]. De gegevens uit hoofdstuk 2 en 4 verschillen aanzienlijk, hetgeen zich laat verklaren doordat de bestudeerde populaties niet overlappen (bijvoorbeeld 'alle type chirurgische opnamen' in hoofdstuk 2 en alleen 'electieve chirurgie' in hoofdstuk 4). Tevens gebruikten we andere methoden om de verschillende groepen te definiëren (in hoofdstuk 2 met behulp van koppeling van de DBCs aan NICE en in hoofdstuk 4 een vergelijking van de gegevens van de NICE database met een ruwe schatting van de Nederlandse Kanker Registratie). Maar beide studies zijn consequent in de conclusies dat vooral slokdarmkanker, alvleesklier/ galwegkanker en CRC geassocieerd zijn met frequente IC opname.

Klinische karakteristieken en mortaliteit van kankerpatiënten opgenomen op de IC

Meerdere publicaties rapporteren een verbetering van ziekenhuissterfte van kritisch zieke kankerpatiënten in de laatste decennia [8, 17-22]. De oorzaak hiervan is niet helemaal duidelijk, maar een zekere rol is weggelegd voor verbeterde IC zorg als zodanig, verbeterde diagnostiek en behandelopties, alsmede een verandering in de triage voor opname op de IC van de oncologische populatie leidend tot selectie van hen met de beste kansen op overleving [6].

De meest recente data aangaande mortaliteit en morbiditeit van kankerpatiënten op de IC zijn gegenereerd op basis van single-center analysen, en veelal in gespecialiseerde (hemato-)oncologische IC's [6]. Een essentieel verschil met deze oudere data en de studies zoals beschreven in hoofdstuk 2-5 van dit proefschrift is dat dit onderzoek gericht is op de uitkomst van kankerpatiënten opgenomen op de algemene IC van de ziekenhuizen in Nederland. De studie beschreven in **Hoofdstuk 3** kan vergeleken worden met twee recentere multicenter studies betreffende uitkomstanalyse van kankerpatiënten opgenomen op algemene IC's [23, 24]. Deze studies verschillen echter kwantitatief met de data weergegeven in Hoofdstuk 3 (respectievelijk > 34,000 versus 473 en 717 kankerpatiënten) en ten aanzien van de periode waarin de data zijn verzameld (respectievelijk vier jaar versus twee weken en twee maanden) [23, 24]. De conclusies van de drie studies laten zich toch goed vergelijken en resumerend kan gesteld worden dat een diagnose van kanker bij opname op de IC niet zeldzaam is en varieert tussen 13.5% (hoofdstuk 3), 15.0% [23] en 21.5% [24]. Uit hoofdstuk 3 blijkt verder dat ongeplande IC opname van kankerpatiënten minder frequent geschiedt (9.5%). Een mogelijke verklaring is dat men minder bereid is kankerpatiënten in acute nood over te plaatsen naar een IC gezien de onderliggende zorgelijke diagnose. Inderdaad blijkt uit de verkregen data in hoofdstuk 3 dat de prognose van kankerpatiënten opgenomen op de IC sterk afhankelijk is van het opna-

Figuur 1: Alternatieve overwegingen voor weigering van IC opname van kankerpatienten die behoefte hebben intensieve zorg en orgaanondersteunende therapie zoals verzorgd op de IC (gereproduceerd uit ref. 6, met toestemming)



	Type IC opname	Klinische situatie
1.	Volldige IC behandeling	Nieuwe kanker diagnose. Maligniteit in complete remissie.
2.	IC - trial	Verwachtingen van gestarte behandeling niet bekend of nog onzeker.
3.	Uitzonderlijke IC opname	Behandeling nog niet getest in een kritisch zieke kankerpatient.
4.	Heroïeke IC opname	Behandelaars zoals (hemato-)oncoloog en intensivist adviseren tegen een IC opname, maar patient en naasten dringen aan.
5.	Suggesties voor andere type IC opnamen	
	IC opname uit voorzorg	IC opname kan, bij eerste presentatie van de maligniteit, kans op orgaan falen beperken/voorkomen. (bijv. tumor-lysis, respiratoire insufficientie).
	Vroege IC opname	Ter voorkoming van snelle verslechtering van orgaanfuncties die al gecompromiteerd zijn. Ter voorkoming van late IC opname (geassocieerd met hogere mortaliteit).
	IC opname ter palliatie	IC opname voor maximaal niet- invasieve- beademing.
	Non-IC zorg op de IC	IC-opname voor korte interventie (verwijdering lijnen, toedienen medicatie).
	IC opname in terminale fase	IC opname is noodzakelijk voor opstarten palliatieve maatregelen en symptoom behandeling.

me type. De mortaliteit van medische (niet-chirurgische) kankerpatiënten is veel hoger dan van medische patiënten zonder kanker. Dit geldt in mindere mate voor de vergelijking tussen chirurgische kankerpatiënten en chirurgische patiënten zonder kanker. Ook in de analyse van Soares is aangetoond dat medische kankerpatiënten een hogere IC- en ziekenhuissterfte kennen (respectievelijk 44% en 58%) dan kankerpatiënten opgenomen op de IC na ongeplande chirurgie (respectievelijk 23% en 37%) ([24]. Hieruit blijkt dat data betreffende morbiditeit en mortaliteit van kankerpatiënten opgenomen op de IC alleen geïnterpreteerd kunnen worden indien informatie over opname type bekend is (gepland of ongepland en medisch versus chirurgisch).

De follow-up van de patiënten in hoofdstuk 3 is beperkt tot de duur van de ziekenhuisopname. Dit criterium wordt veelal gebruikt in de bestudering van deze populatie. Kennis over de impact op overleving, morbiditeit en kwaliteit van leven op langere termijn na IC opnames van oncologische patiënten is veel beperkter. Data zoals tot heden gepubliceerd suggereren een toename van mortaliteit van kankerpatiënten tot meerdere jaren na opname op de IC, in vergelijking met patiënten zonder kanker met dezelfde leeftijd, en geslacht [25-27]. Ook de recent gepubliceerde data uit Nederland betreffende een 3-jaars follow-up na IC opname tonen aan dat de groep van kankerpatiënten een bijna twee maal zo hoge mortaliteit hebben dan andere IC populaties [28]. Uit **Hoofdstuk 2** blijkt tevens dat kankerpatiënten die opgenomen zijn op de IC een veel slechtere overleving hebben dan kankerpatiënten die niet op een IC opgenomen zijn.

Chirurgische kankerpatiënten op de IC

In de laatste jaren worden steeds meer kankerpatiënten opgenomen op de IC na grote oncologische operaties. Het type operatie voor de verschillende maligniteiten verschilt uiteraard met een eigen risico op postoperatieve complicaties en noodzaak van intensieve zorg. Vele studies hebben gerapporteerd over postoperatieve morbiditeit en mortaliteit in een ongeselecteerde chirurgische groep [29-33]. Minstens zoveel data zijn beschikbaar over postoperatieve mortaliteit na electieve oncologische chirurgie [34-40]. Echter, er is slechts beperkte informatie over het effect van IC opname na electieve kankerchirurgie. De enige studie tot heden, gepubliceerd in 2010, maakte geen onderscheid tussen het type kanker en operatie en betrof maar 381 patiënten. De mediane IC opnameduur was 2 dagen en de IC mortaliteit was 6% [24]. In **Hoofdstuk 4** worden unieke data van bijna 29,000 patiënten geanalyseerd met betrekking tot morbiditeit en mortaliteit na electieve oncologische chirurgie opgenomen op de IC. De ziekenhuismortaliteit voor de verschillende type oncologische chirurgie komt overeen met eerdere publicaties betreffende chirurgie voor longkanker [41], slokdarmkanker [42, 43], pancreas [44], gynaecologische tumoren [45], blaaskanker [46] en KNO-tumoren [47, 48]. In hoofdstuk 4 wordt duidelijk dat ongeveer een kwart van de patiënten die een electief oncologische operatie ondergaan CRC hebben, maar dat bij een significant deel (één derde) de indicatie voor IC opname pas tijdens of na de operatie gesteld wordt. In **Hoofdstuk 5** ligt het accent op spoedoperaties van patiënten met CRC. Deze analyse is van actuele waarde daar recente data uit Groot-Brittannië aantonen dat een kwart van de patiënten met dikke darm kanker zich in een spoedsituatie presenteren en acuut geopereerd moeten worden [49], terwijl duidelijk is dat een spoedlaparotomie voor CRC een negatieve impact heeft op de overleving [50, 51]. We beschrijven in hoofdstuk 5 een hoge IC en ziekenhuis sterfte (respectievelijk 10% en 22%) na CRC spoedchirurgie. Dit is in overeenstemming met eerdere publicaties [50, 51]. Overigens

bleek er geen verschil in ziekenhuissterfte van patiënten die een spoedoperatie ondergaan voor CRC of om andere redenen; de IC sterfte was juist wat lager. De patiëntenpopulatie voor deze analyse kenmerkt zich door spoedchirurgie en spoed IC opname. Wij gebruikten geen gegevens van patiënten die niet postoperatief werden opgenomen op de IC en een vergelijking met deze groep is derhalve niet mogelijk. De beslissing om patiënten op te nemen op een IC is deels subjectief en kan verschillen per ziekenhuis of regio. De beschreven resultaten dienen in deze context geïnterpreteerd te worden.

Infecties bij patienten met kanker

Infecties bij patiënten met een oncologische aandoening zijn vaak de oorzaak van een verlengde ziekenhuisopname [52]. Kanker is geassocieerd met een hogere kans op bacteriëmie en sepsis [53-55] en deze systemische infecties zijn een belangrijke doodsoorzaak bij kankerpatiënten [56-58]. Er is veel onderzoek gedaan naar de impact op morbiditeit en mortaliteit van infecties door de verschillende micro-organismen bij kanker patiënten. Daaruit komt naar voren dat niet alleen banale micro-organismen tot ernstige schade kunnen leiden, maar ook laag virulente verwekkers, zoals enterococcen, hebben een significante invloed op morbiditeit en mortaliteit in deze kwetsbare populatie [59, 60]. In verschillende hoofdstukken van dit proefschrift wordt aandacht besteed aan de rol van infecties bij kankerpatiënten. Uit **Hoofdstuk 3** blijkt dat ongeveer een derde van de niet chirurgische kankerpatiënten die acuut op de IC opgenomen wordt een gedocumenteerde infectie heeft, wat veel meer is dan bij de niet oncologische patiënten. In hoofdstuk 5 blijkt dat bij één op de tien patiënten opgenomen op de IC na spoedchirurgie voor CRC een sepsis wordt gedocumenteerd. Uit de resultaten in **Hoofdstuk 6** blijkt dat Gram-positieve bacteriën het meest vertegenwoordigd zijn in bloedkweken van zowel kankerpatiënten als patiënten zonder kanker, hetgeen overeenkomt met eerdere publicaties [61-64]. Wij vonden echter geen relatie met het risico op een bacteriëmie met een specifieke verwekker, zoals eerder werd beschreven voor *S. aureus* [65], *E. coli* [66] en *K. pneumoniae* [67]. Alleen voor *P. aeruginosa* bleek een relatie met kanker, zoals eerder gerapporteerd [68]. Het lijdt geen twijfel dat veroorzakers van bacteriëmie en dientengevolge de morbiditeit kan verschillen tussen de ziekenhuizen, afhankelijk van patiëntenpopulatie, type ziekenhuis (oncologisch centrum, transplantatie-unit of algemeen ziekenhuis) en het spectrum van antibiotica resistentie in het betreffende instituut.

In **Hoofdstuk 7** bestuderen we het infectie- en complicatierisico van het gebruik van centraal veneuze lijnen, in het bijzonder PACs, in kankerpatiënten en niet-oncologische patiënten. PACs worden frequent gebruikt bij patiënten met noodzaak tot veneuze toegang voor intraveneuze medicatie, zoals chemotherapie en ondersteunende zorg. Een opvallende bevinding in deze studie is dat kankerpatiënten een minder grote kans hadden op verwijdering van de PAC als gevolg van een infectie dan niet kankerpatiënten ondanks hun grotere kwetsbaarheid als gevolg van de verminderde weerstand voor infecties. De beste verklaring hiervoor lijkt het feit dat vooral verpleegkundigen op (hemato-)oncologie afdelingen veel ervaring hebben met PACs en kwetsbare patiënten, in tegenstelling tot verpleegkundigen op andere afdelingen in het ziekenhuis, waar patiënten met PACs veel minder frequent gezien en behandeld worden. De incidentie van PAC infecties in deze analyse (11.8%) is vergelijkbaar met eerdere studies en publicaties [69-71]. Ook de veroorzakende micro-organismen (veelal coagulase negatieve stafylokokken en *S.aureus*) komen overeen met eerdere data [71, 72].

Invloed van geslacht

Geslacht kan van invloed zijn op de aard van de complicaties en therapeutische interventies op een IC. Hoewel de totale IC sterfte niet verschilt tussen mannen en vrouwen [73, 74], hebben mannen een grotere kans op sepsis [74-76]. Tevens vinden bij de mannen vaker therapeutische interventies plaats op de IC dan bij vrouwen [73, 77]. In dit proefschrift hebben we de impact van geslacht op de verschillende uitkomstparameters bij kankerpatiënten in kaart gebracht. Uit **Hoofdstuk 2** blijkt dat meer mannen dan vrouwen met kanker werden opgenomen op de IC terwijl de bestudeerde oncologische populatie uit meer vrouwen bestond. Dit kan deels verklaard worden door het feit dat de prevalentie van borstkanker bij vrouwen hoog is, deze patiënten lang leven en zij maar zelden op de IC worden opgenomen. Voor nagenoeg alle kankerdiagnosen afzonderlijk vonden we een hoger percentage mannen opgenomen op de IC dan vrouwen met uitzondering van slokdarmkanker. Deze bevinding staat niet op zichzelf, ook uit andere studies blijkt een discrepante verhouding in IC zorg en opname tussen mannen en vrouwen [73, 77-79]. Tot heden is hiervoor geen goede verklaring gevonden, een goede reden voor verder onderzoek. In **Hoofdstuk 5** werd op basis van voorgaand onderzoek [80-83] verwacht dat geslacht van invloed is op het ziektebeloop en mortaliteit van acute CRC chirurgie. Behoudens een klein geslachtsverschil in mortaliteit bij patiënten die een spoedlaparotomie ondergingen voor andere indicatie dan CRC, was de impact van het geslacht minimaal, ook na correctie voor andere co-variabelen.

Suggesties voor de toekomst

De kennis over de karakteristieken van kankerpatiënten opgenomen op de IC is inmiddels uitgebreid. De meeste studies betreffen retrospectieve onderzoeken met een case mix van chirurgische en niet-chirurgische kankerpatiënten en een diversiteit van oncologische diagnosen zoals solide tumoren, hematologische maligniteiten en patiënten die een beenmerg transplantatie hebben ondergaan. De resultaten van deze studies zijn moeilijk te vergelijken als gevolg van variatie in criteria voor IC opname en ontslag, voor palliatieve maatregelen en voor besluitvorming ten aanzien van terminale zorg. Er zijn dus nog heel wat actuele onderzoeksvragen aangaande de impact van een IC opname op verschillende oncologische patiëntenpopulaties, vooral onderzoek bij patiënten die om andere reden opgenomen worden dan direct postoperatieve zorg. Een van de meest relevante vragen betreft de lange termijn effecten en overleving van kankerpatiënten na IC opname. Het is van grote waarde te kunnen onderbouwen of de IC opname uiteindelijk leidt tot een verbeterde overleving met acceptabele kwaliteit van leven. Verder onderzoek naar kwaliteit van leven en fysieke conditie in de jaren na de IC opname is hiervoor van belang. Kortom: wat is de patiënt (en de familie) er mee opgeschoten dat er een high-impact verblijf op de IC heeft plaatsgevonden? En belangrijk, kan deze patiënt uiteindelijk weer verder behandeld worden met bijvoorbeeld chemotherapie en bestraling ter verbetering van de oncologische conditie?

Dus verder onderzoek is noodzakelijk naar voorspellende factoren die de kans op sterfte op de IC van kankerpatiënten beter in kaart brengen. Factoren die een belangrijke rol speelden in het verleden, zoals neutropenie, hoeven niet meer actueel te zijn. Initieel werd neutropenie als een klassieke voorspeller van mortaliteit gezien [84], maar inmiddels bevestigen meerdere studies vanuit verschillende continenten (België en Brazilië) dat de IC sterfte niet meer gecorreleerd is aan neutropenie [85] [24]. Andere klassieke variabelen zoals leeftijd en type kanker zijn

ook niet meer consequent gerelateerd aan een hogere IC sterfte. Deze wordt namelijk vooral beïnvloed door de IC opname criteria [6], terwijl IC opname op haar beurt weer sterk beïnvloed wordt door de verdere ontwikkeling van minder invasieve procedures voor grote oncologische problemen, bijvoorbeeld laparoscopische ingrepen bij abdominale maligniteiten en de recent ontwikkelde endoscopische slokdarmresecties [86].

Al met al is er een toenemende behoefte aan adequate opname criteria voor kankerpatiënten op de IC. De balans tussen (niet-)invasieve behandelingen en voorkomen dat er onnodig uitstel optreedt van optimale therapie is kwetsbaar. Dit geldt vooral voor de oncologische populatie. De huidige triagecriteria voor IC opname kunnen hier ter discussie worden gesteld. In een recente publicatie is inderdaad aangetoond dat 20% van de kankerpatiënten die afgewezen werden voor IC opname om reden van een te goede conditie, uiteindelijk toch overleed in het ziekenhuis (veelal nog na een uitgestelde IC opname), terwijl 25% van de kankerpatiënten die geweigerd werden om redenen van een te slechte conditie uiteindelijk overleefden [87]. Uitgestelde IC opname (of late IC opname) van kankerpatiënten met multipel orgaan falen heeft een slechte prognose, waarbij het type en aantal organen dat faalt een goede voorspellende waarde hebben voor sterfte [15, 21]. Hoewel vroege IC opname de kans op sterfte vermindert [18], zal voor de oncologische populatie de criteria nog verder uitgewerkt moeten worden door bijvoorbeeld in onderzoek verband te randomiseren tussen vroege IC opname (bij falen van één orgaansysteem) versus geen IC opname of verlate IC opname. Een goede klinische conditie van de patiënt voor start van de acute verslechtering leidende tot noodzaak van IC opname, geeft de beste kans op overleving op de IC [88]. Het is overigens niet duidelijk of de conventionele performance scores zoals gebruikt in de objectivering van de oncologische patiënt (bijvoorbeeld Karnofsky-status of WHO performance score) een meerwaarde hebben om het succes van een IC opname te bepalen. De eerder genoemde “ICU-trial”, waarbij na drie dagen van IC zorg opnieuw wordt beoordeeld of de conditie van patiënt ten goede verandert (doorzetten intensieve zorg) of verslechtert (stop intensieve zorg), kan een geschikter instrument blijken om patiënten met kanker de maximale mogelijkheid tot herstel te bieden [12, 15]. De duur van een dergelijke “proefperiode op de IC” kan verder onderzocht worden, daar een verslechtering van de klinische toestand van patiënt uiteindelijk zal leiden tot een dialoog ter introductie van de terminale fase, met alle consequenties voor patiënt en familie [89]. Deze veranderde instelling van de zorggevers op de IC naar de patiënt en familie heeft veel implicaties. Gesprekken over beëindiging van orgaanfunctie vervangende therapieën en andere ondersteunende maatregelen, dienen helder en duidelijk te geschieden. Samenspraak tussen intensivisten en de oncologisch verantwoordelijken is onontbeerlijk. Protocollen, geïmplementeerd om de kwetsbare dialoog aangaande reanimatie codes en consequenties van maximaal ondersteunende therapieën tussen patiënt, naasten en behandelaars, structuur te geven zijn onontbeerlijk. In geval van acute verslechtering van een dergelijke patiënt behoort het spoed-interventie team van het ziekenhuis hierover goed geïnformeerd te worden en dit team kan beslissen een patiënt vroeg in het beloop over te plaatsen naar de IC. Een goede, ziekenhuis brede, set van afspraken is hiervoor belangrijk. Indien een patiënt met kanker is opgenomen op de IC is dagelijks overleg tussen intensivist en oncologisch specialist vanzelfsprekend. De intensivisten behoren geïnformeerd te worden over het beloop van de kanker en het behandelperspectief van de patiënt wanneer hij of zij voldoende hersteld is. Indien een kankerpatiënt nog niet door de IC wordt overgenomen maar ernstig ziek is, zal de medische en verpleegkundige staf zich hiervan goed bewust moeten blijven. Klinische evaluatie door de ver-

antwoordelijke specialist (al of niet begeleid door arts-assistenten) van de vitale parameters en verschillende orgaansystemen, is geïndiceerd. Zo kan een snelle verslechtering geconstateerd worden en leiden tot tijdige overplaatsing naar de IC.

In dit proefschrift is niet ingegaan op de mogelijkheid om intensieve kankertherapieën, zoals chemotherapie, te combineren met een verblijf op de IC. Uit de studies betreffende deze problematiek kan worden opgemaakt dat toedienen van chemotherapie op de IC mogelijk is en niet leidt tot hoge mortaliteit of onverwachte morbiditeit [90, 91]. Bovendien lijken kankerpatiënten met een septische shock na chemotherapie een betere korte termijn prognose te hebben dan septische kankerpatiënten zonder chemotherapeutische behandeling [90, 91]. Hoewel NICE veel informatie bevat over de meerderheid van de Nederlandse IC patiënten, wordt specifieke oncologische informatie en dus verstrekking van chemotherapie op de IC, niet geregistreerd. Daar de NICE database op zichzelf staat en niet gelinkt is met bijvoorbeeld de ziekenhuisapotheek, is inzicht in cytostaticaverstrekkingen op de IC niet goed mogelijk. Tegenwoordig worden veel kankerpatiënten intensief, multidisciplinair, behandeld ter vergroting van de kans op curatie. Inzicht in effecten van deze therapieën op uitkomst van de IC opname is van groot belang, niet alleen voor intensivisten, maar ook voor alle oncologisch specialisten zoals medisch oncologen, hematologen, radiotherapeuten en oncologisch chirurgen.

Ter afsluiting kunnen we stellen dat de overleving van patiënten met kanker opgenomen op de IC allengs toeneemt als gevolg van verbeterde oncologische behandelingsstrategieën en ondersteuning op de IC. Het managen van kritisch zieke kankerpatiënten op de IC eist een speciale instelling van de intensivist en een nauwe samenwerking tussen hen en oncologisch specialisten. Goede afspraken onderling zullen een positieve impact hebben op de kansen van de patiënt met een maligniteit. De kankerspecialisten behoren de staf van de IC goed te informeren over de curatieve behandelopties en prognose van de kwaadaardige ziekte. Op hun beurt, kunnen intensivisten, weer beter de prognose van een patiënt met acuut (multi-)orgaanfalen inschatten. Opname op de IC is een gezamenlijke beslissing van intensivist, oncologisch specialist en uiteraard de wil van de patiënt en naasten. Beslissingen betreffende niet gebruiken of staken van orgaanfunctie vervangende therapieën moeten in gezamenlijkheid genomen worden, en de informatie naar patiënt en naasten zal door beide medisch specialisten uitgedragen moeten worden. Een verdere uitbreiding van de samenwerking tussen beiden behandelaars is eminent, mede daar uitbreiding van expertise een verbetering en optimalisering van de zorg van deze bijzondere patiëntenpopulatie in onze ziekenhuizen garandeert.

Referenties

Zie de referenties van Hoofdstuk 8.

ADDENDUM

Monique M.E.M. Bos

Woord van Dank

Graag wil ik beginnen met een woord van dank aan mijn promotor en vriend Evert de Jonge. De ‘eeuwige discussie’ of patiënten met kanker nu wel of niet direct naar de IC gebracht moeten worden heeft voor ons in ieder geval tot deze dissertatie geleid. Wat enigszins laconiek begon, leidde snel tot verder onderzoek en vraagstellingen over alle aspecten van de presentatie van kankerpatiënten op de IC. Jouw inspiratie, overzicht en optimisme hebben tot het volbrengen van dit proefschrift geleid. Mijn wetenschappelijke lag-time betrof precies twee weken, het interval waarin wij elkaar op jouw kamer in het LUMC troffen om de voortgang te bespreken en ik weer vol enthousiasme en vertrouwen verder kon. Je scherpe en eerlijke analyses van de problemen waarop wij stuitten zijn een verademing geweest. Ik heb een enorm respect gekregen voor je kennis, vermogen van multitasking als clinicus en hoofd van een complexe afdeling als een IC in een academische setting, naast je directoraat van de NICE. Ik wens je voor nu heel veel plezier in je nieuwe huis, dat tussendoor ook nog even gekocht en verbouwd werd.

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Mijn moeder wil ik hier niet vergeten, dank voor alle relativering, maar toch ook veel steun. Ik kom nu weer vaker naar Brabant en weet heel goed dat mijn vader trots en blij was geweest dat de "s" is weggewerkt.

Helen en Lara. Nu is het klaar en het argument "mamma heeft geen tijd, ze moet promoveren" kan van tafel. Let op, zoals beloofd en dus nu opgenomen in het boek: "Heel veel dank voor jullie geduld en begrip om mij dit boekje te laten schrijven in de weekenden en vakanties van de afgelopen periode". Maar jullie mogen best weten dat alle voorgaande pagina's niets voorstellen ten opzichte van mijn dankbaarheid voor jullie bestaan; wat een geweldige meiden zijn jullie!

En de laatste woorden voor Tommie, mijn echtgenoot en steun. Zonder jou was dit proefschrift er niet gekomen….de rust en vanzelfsprekendheid waarmee je vast stelde dat het wel goed komt met al die tabellen en artikelen was fijn. Maar veel fijner is het dat je bij mij hoort, van mij bent en met mij deelt wat echt belangrijk is…en dat staat niet op papier.

Curriculum Vitae

Monique Martina Elisabeth Maria Bos werd geboren op 23 december 1961 in Heeze (NBr). Na het behalen van het VWO diploma aan het Strabrecht College te Geldrop startte zij in 1980 met de studie Geneeskunde aan de Universiteit van Amsterdam. De doctoraalfase combineerde zij met een studentassistentschap anatomie en parttime werk als hostess voor de Amerikaanse Ambassade. In 1986 behaalde zij haar artsexamen (cum laude) en startte met de opleiding interne geneeskunde aan de Vrije Universiteit van Amsterdam (opleider Prof. Dr. J. van der Meer). De eerste twee jaar hiervan vonden plaats in de Maria-Stichting te Haarlem (opleider Dr. S.C. Reinders Folmer). Daar maakte zij voor het eerst echt kennis met de zorg voor kankerpatiënten, en raakte geïnspireerd en geënthousiasmeerd voor de oncologie door o.a. Dr. C.A. de Swart en later in de opleiding door Prof. Dr. H.M. Pinedo. In juni 1993 vond de registratie als internist plaats.

Van juni 1993 tot augustus 1996 volgde de subspecialisatie medische oncologie, die werd gedaan in Memorial Sloan-Kettering Cancer Center, New York, Verenigde Staten (Dr. G.J. Bosl, medical director fellowship program MSKCC), gevolgd door een korte hernieuwde kennismaking met de Nederlandse oncologie in het Antoni van Leeuwenhoek ziekenhuis te Amsterdam (opleider Prof. Dr. S. Rodenhuis).

Vanaf september 1996 is zij als internist-oncoloog verbonden aan het Reinier de Graaf Gasthuis te Delft. Sinds 2005 is zij tevens medisch coördinator van de oncologische zorg van dit ziekenhuis en als zodanig toegevoegd aan het management. Participatie in de leergang “Management voor Medici” (Tias Bussiness School, Universiteit van Tilburg, 2004-2005, Prof. Dr. J. Moen) en het “Program for Health Care Executives” (Harvard School of Public Health, Boston, Verenigde Staten, 2006) boden hiervoor een basis. Haar professionele hartstocht ligt in het organiseren en verbeteren van de logistiek en infrastructuur voor multidisciplinaire zorg van kankerpatiënten.

In 2009 ondernam zij, samen met Prof. Dr. E. de Jonge (Intensive Care Geneeskunde, LUMC), de eerste stappen om tot deze dissertatie te komen.

Zij is sinds 1993 getrouwd met Tom van der Poll en heeft twee dochters Helen (1995) en Lara (1998).

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