INTRODUCTION

CHAPTER 1

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Based in part on:
Patients with cancer on the ICU: the times they are changing
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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

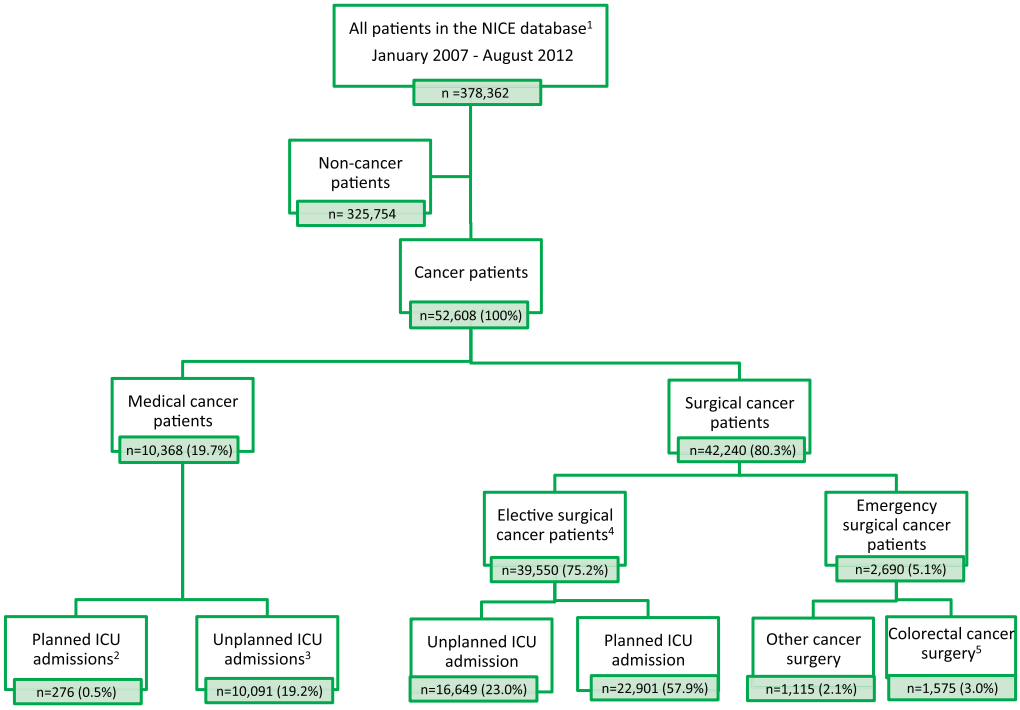
The *general objective* of the research presented in this thesis is to obtain more insight in the occurrence and outcome of acute critical illness in patients with cancer.

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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