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SUMMARY, GENERAL DISCUSSION & FUTURE PERSPECTIVES

CHAPTER 8

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

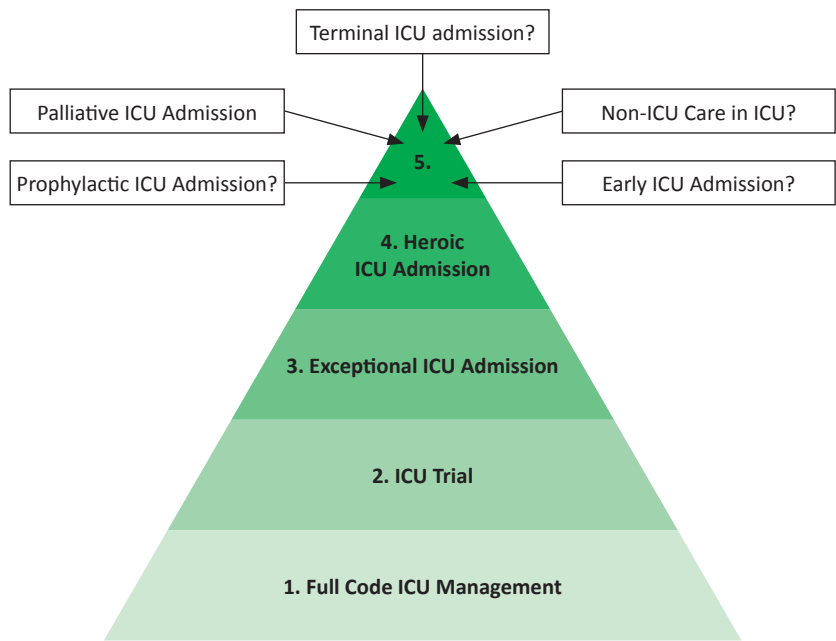
supportive therapy in cancer patients with life threatening conditions due to their disease or treatment [6, 7]. Some investigators even defined ICU admission after 1996 as an independent predictor for a better outcome of cancer patients in the most recent decade [8, 9]. Factors that likely have contributed 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 al. 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 appropriate, 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 disturbances, 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 antibiotics 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-cholangio-carcinoma 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 than 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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