Admission of patients with solid cancer in the Intensive Care Unit: Challenging situations

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SUMMARY

The proportion of cancer patients considered for admission in intensive care units (ICU) gradually increased over the last decades. In this situation, it is important to avoid inappropriate management, whether through refusal of admission that could be beneficial, or through futile therapeutic escalation. In this review, we describe the factors that medical oncologists and intensive carers should discuss when considering ICU admission for cancer patients and propose a framework for decision-making based on four important concepts. Among cancer patients, data strongly suggest that the short-term prognosis is more linked to the acute pathology than to the underlying active tumour. More specifically, the impairment of more than two vital organs and the requirement of organ support are the most important factors predictive of mortality. ECOG performance status furthermore remains a crucial prognostic factor to consider. Open discussions with patients and close relatives at cancer diagnosis and during treatment are mandatory for informed decision making during an acute event.

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INTRODUCTION

Determining the potential benefits of intensive care unit (ICU) admission for patients with solid cancer is a complex challenge. This question frequently requires input from physicians from different specialties. This review aims to summarise the current knowledge and recent research on this topic.

MAIN SECTION

EPIDEMIOLOGY OF ONCOLOGICAL PATIENTS IN ICU

In Belgium, in 2020, over 74,000 new cases of cancer were diagnosed, and more than 472,000 individuals were living with cancer, representing 4.1% of the Belgian population.[1] On average, 5 to 10% of patients in oncology and haematology are admitted to the ICU within the first two years following a cancer diagnosis.[2]

Continuous education of ICU staff on the specificities of cancer patients is required as the fast-expanding development of new anticancer treatments allows for an improvement in the prognosis of these patients, but at the cost of new and sometimes severe toxicities. Chemotherapy-related adverse events vary according to the cytotoxic compound but frequently consist of asthenia, and digestive (*e.g.*, colitis), haematological (*e.g.*, cytopenia), and neurological (*e.g.*, peripheral neuropathy) toxicities. Immunotherapy is generally better tolerated but can be complicated by a wide range of immune-mediated side-effects, among which skin, endocrine, digestive, and pulmonary toxicity are the most frequent.

In the 1990s, the ICU mortality rate for solid or haematologic cancer patients was around 90%, leading to general reluctance to admit such patients, as recommended by the American College of Critical Care Medicine at that time.[3]

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However, with the improvement of anticancer therapies and intensive care management, this mortality rate has significantly decreased over the past thirty years. As a seminal example, immunotherapy, and more specifically checkpoint blockade inhibitors targeting CTLA-4 and PD(L)1, dramatically enhanced the management of patients with advanced melanoma. The median survival of these patients reached six to twelve months before their introduction, but now improved to four years. Importantly, a substantial percentage of patients remain progression-free after discontinuation of their treatment.[4]

Three scenarios can lead to the management of patients with cancer by intensive care physicians:

1. Planned admission, such as postoperative monitoring following oncological surgery.
2. Unplanned admission due to acute cancer- or treatment-related complication, or due to an acute independent condition (*e.g.*, sepsis).
3. Initial ICU admission revealing a previously unknown cancer (for example, a seizure revealing brain metastases from a previously unknown cancer).

These different situations are common and carry varying levels of morbidity and mortality depending on the context.

An observational study conducted in the Netherlands between 2006 and 2011 showed that among 36,860 patients with cancer, 6.4% were admitted to ICUs, primarily within the first two years of their diagnosis.[2] More than half (56%) of them were admitted after surgery. The 44% admitted to ICUs on an unplanned basis mainly suffered from sepsis. Among all oncological cases in the hospital, the risk of being admitted to the ICU was higher for patients with esophageal, colorectal, and pancreatic cancer.

In 2008, in an observational study analysing all patients admitted to ICUs across Europe over a fifteen-day period, 15% of them were suffering from cancer, with a majority (85%) having solid tumours.[5] It is important to distinguish between malignant haematological diseases and solid tumours, given the significant difference in prognosis and management between these two entities. In this study, patients with solid tumours admitted to ICUs were generally older and suffered more from respiratory failure or sepsis than patients without oncological diseases. Among patients admitted to ICU for post-operative monitoring, most patients suffered from a solid tumour. However, there were no differences in morbidity severity based on the SOFA score (described below) between the oncological and the non-oncological populations.

OUTCOMES OF THE ONCOLOGICAL PATIENTS IN ICU

Various scoring systems, including the APACHE II and SAPS II scores, assess severity and mortality risk at ICU admission.[6,7] They are calculated within the first 24 hours of admission to the ICU, based on the type of admission (medical or scheduled- or unscheduled-surgical admission) and on physiological (age, chronic disease), biological (blood urea, sodium, potassium, and bicarbonate levels, white blood count), and parametric values (heart rate, systolic blood pressure, temperature, and urine output). These scores quantify the severity of the condition and the mortality risk. The SOFA score is calculated daily starting at ICU admission, based on organ failures.[8] It allows tracking the evolution of the morbidity severity of the patients during their stay. This score is based on six sub-scores, one for each organ system: respiratory (PaO_2/FiO_2 ratio), neurological (Glasgow Coma Scale score), renal (creatinine level and/or urine output), cardiovascular (blood pressure or need for vasopressors), haematological (platelet count), and hepatic (bilirubin level).

In the European observational study of 2008, survival was similar between oncological and non-oncological populations when no more than two organs were affected, with a 27% hospital mortality rate.[5] However, mortality significantly increased among cancer patients when three or more organs were involved, with a mortality rate of 75%, compared to 50% in the non-oncological group. In this study, predictive factors of mortality among oncological patients included the SAPS II score, sepsis, respiratory impairment, and the need for mechanical ventilation.

Over the years, the number of admissions of cancer patients to ICUs has increased, including a significant rise in those with metastatic cancer.[9] Admissions related to treatment side effects have also risen in parallel with the development of new therapies. Despite the broadening of admission criteria for cancer patients in the ICU, a French retrospective study showed that the survival of these patients at ICU discharge and at one year remained unaffected.[9] This study suggests that among ICU-admitted cancer patients, irrespective of metastatic status or treatment-related toxicity, short-term prognosis is more linked to the acute pathology than to the underlying active tumour.

The Respiratory Research Group in Onco-haematology (Grrr-OH) studied patients with solid tumours admitted to the ICU for medical reasons or urgent operative management.[10] Based on their study, they proposed the "oncoscore," determined by cancer type (lung, breast, colorectal, or other),

metastatic status, and type of organ support required in ICU (mechanical ventilation, inotropes, extracorporeal renal replacement therapy). These independent factors are associated with patient mortality at 120 days after ICU discharge. In this retrospective study, patients with metastatic lung cancer requiring organ support had a higher mortality rate at 120 days. Further prospective studies are warranted to validate this score and elucidate the impact of various independent factors on ICU-surviving cancer patients' mortality.

Based on various studies, it appears that the presence of metastases alone does not solely determine the outcome of oncologic patients admitted to the ICU, although the studies are sometimes discordant in their results.[9-13]

As in the general population, the patient's physiological state prior to ICU admission is an important determinant of outcome. Poor performance status (measured by the ECOG performance status) is independently associated with short- and long-term mortality.[14]

Despite the selection bias inherent to retrospective and observational studies, the available data clearly suggest that the notion of cancer should not be the determining factor for accepting or refusing ICU admission. Short-term survival is mainly determined by the acute pathology that brings the patient to the ICU and by associated organ dysfunctions.[15]

In addition to mortality during or following care in the ICU, present and future quality of life, and the possibility to continue the oncological treatment are two important factors to consider during the same discussion. To our knowledge, no large study has clearly determined the proportion of patients requiring a change in cancer treatment after ICU stay. However, a monocentric case series of severely affected advanced lung cancer patients admitted to ICU (67% of patients with ECOG performance status ≥ 2, 90% requiring mechanical ventilation) perfectly illustrates these multiple factors to consider, as 78% of patients died in the hospital, and only 52% of the surviving patients received further chemotherapy.[16]

Three scenarios may lead to considering an adaptation of the oncological treatment after the ICU stay:

1. Oncological progression leading to ICU admission.
2. Treatment-related side effect leading to ICU admission.
3. Inability to continue anticancer treatment after ICU stay (renal failure, polyneuropathy, *etc.*).

The patient's quality of life is also an essential factor to consider when health deteriorates and a stay in the ICU is required.[17] Prolonged immobilisation in the ICU often results in muscle loss and varying degrees of polyneuropathy, accompanied by long-term physical consequences like fatigue, loss of independence, and inability to perform daily activities. Studies underscore the importance of physiotherapy in ICU and post-hospitalisation rehabilitation to restore pre-ICU physical status.[18,19]

Finally, ICU stays are emotionally challenging, both for patients and families.[20] In addition to physiological consequences, the patient may experience acute and long-term neuropsychological effects, such as post-traumatic stress disorder (PTSD), sleep disturbances, concentration difficulties, anxiety, and chronic pain. In a multi-centric prospective cohort study, one year after an ICU stay, 30% of patients still complained of depression, even though these patients had no known psychiatric disorders prior to their ICU stay.[21] The incidence of depression was four times higher than the incidence of PTSD in this study, suggesting the correlation between physical disability and depression. Physical rehabilitation could play an important role in preventing these neuropsychological consequences. Early diagnosis and treatment of delirium, acute pain, and agitation might also mitigate their development.[19] Increasingly, ICU clinicians and (para-) medical staff are aware of the importance of good communication with patients and families, considering psychosocial, economic, and spiritual aspects.[22] Data also suggest that the long-term effects following a stay in ICUs are more pronounced in elderly, frail, and co-morbid patients.[20]

A POSSIBLE ALGORITHM TO CONSIDER ICU ADMISSION FOR PATIENTS WITH CANCER

Not all critically ill cancer patients will benefit from ICU admission. Therefore, it is crucial to establish an individualised therapeutic plan for each patient. Assessing whether a patient should be admitted to the ICU, and if so, whether any therapeutic limitations should be considered, is complex. A study conducted in 2001 at a specialised centre showed the imprecision of intensive care physicians' judgement regarding the life expectancy of patients with solid or haematologic cancers who are being considered for ICU admission: at 30 days, 21% of patients deemed 'too fit' for ICU admission had died, while 26% of those judged 'too sick' survived.[23]

When deciding whether to admit or not a cancer patient to the ICU, four criteria should be considered based on the previous data: their overall condition (which can be assessed by ECOG performance status and blood albumin levels), the reversibility of the acute pathology, the prognosis of the underlying tumour disease, and the patient's preference. *Figure 1* shows a schematic admission decision algorithm. *Table 1* summarises the four groups that cancer patients can be divided into.

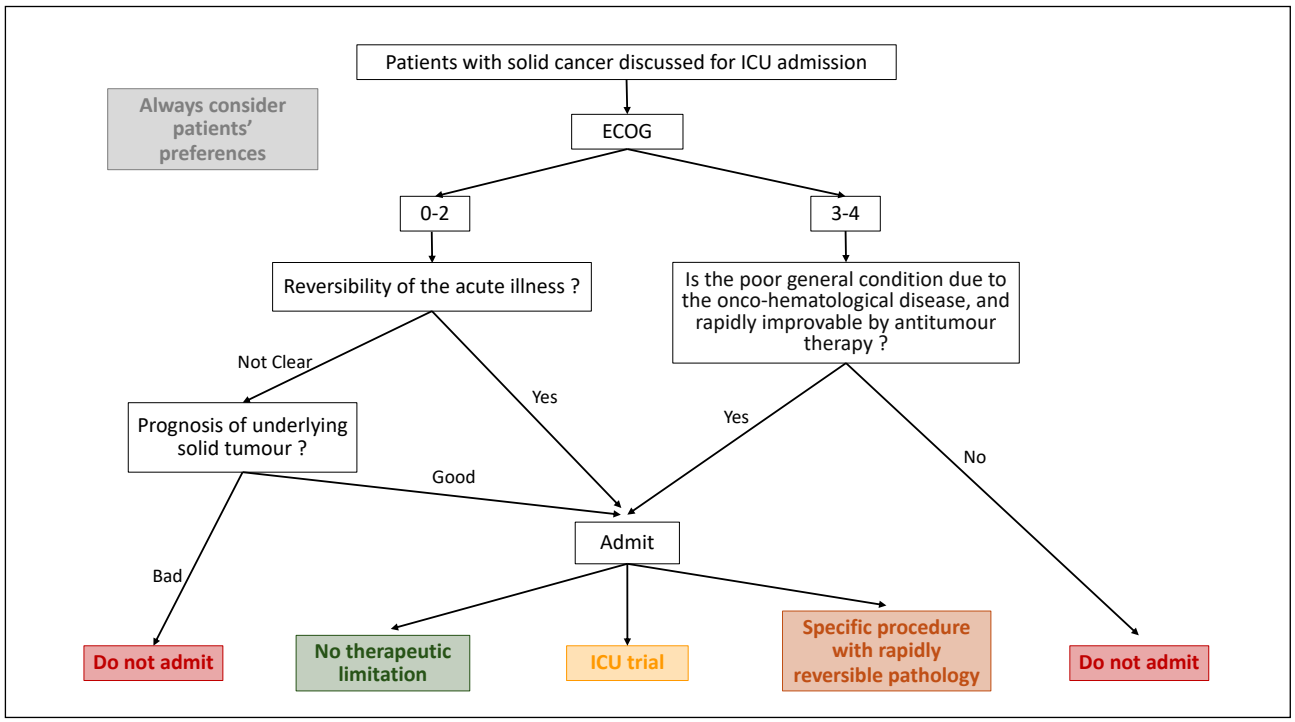

FIGURE 1. A schematic admission decision algorithm.

In some onco-haematology patients, the criteria for ICU admission may be biased, and it is often difficult to determine whether intensive care will be beneficial or detrimental to the patient. The concept of the "ICU trial" is a recently developed approach specifically tailored to patients with such uncertain outcomes.[24] It involves admitting the patient to the ICU for "unlimited" management for a "limited" period. Upon admission to the ICU, treatment goals are established along with a timeframe for their achievement. The patient is then treated intensively, and the situation is reassessed, after five to seven days of management (a predetermined duration decided upon ICU admission). Indeed, studies have shown a marginal survival in cancer patients requiring more than three days of mechanical ventilation, as well as a correlation between organ dysfunctions and outcomes on day five of ICU admission.[25,26] If treatment goals remain unmet despite intensive care, therapeutic de-escalation is considered. A crucial aspect of implementing the ICU trial strategy is to engage in a transparent discussion with patients and their families prior to admission, outlining the goals and subsequent reassessment processes. Further studies are needed to confirm the utility of the ICU trial for cancer patients, compared to specific ICU admission criteria. The optimal duration of intensive treatment before re-evaluation remains uncertain but must be tailored to each specific situation.

Furthermore, recent recommendations advocate for early ICU admission of oncology patients, at the onset of organ dysfunction, when the acute illness requires close monitoring and management, and when the medium to long-term prognosis appears favourable.[27]

DISCUSSING AND ANTICIPATING ARE KEY FOR EFFECTIVE DECISION-MAKING

The evidence clearly suggests that the presence of active cancer should not be considered as the key factor to decide whether to admit a patient to the ICU, especially if the disease is not at an advanced stage. However, to date, this recommendation predominantly relies on observational data. Therefore, establishing clear criteria for limiting treatment in cancer patients potentially requiring ICU admission remains challenging. Given this challenge, open and informed discussions with patients, their families, and treating healthcare specialists are essential.

Communication with patients, close relatives, and other carers is of utmost importance. Patients should, all along their disease course, through open discussions with their treating oncologist, always have an informed view regarding the severity of their tumour disease, treatment options, and associated risks.[13] This will ensure that patients' preferences, treatment adherence, and considerations for palliative care, if applicable, are well understood. It furthermore facilitates more straightforward discussions about intensive care and its implications, particularly in emergency situations. With the patient's consent, close relatives should be informed on the tumour's nature, stage, treatments, and prognosis. Close carers play a crucial role supporting the patient and may also experience significant distress during critical events.

TABLE 1. Patients with solid cancer proposed to ICU can be divided into 4 groups

Group	Description
Admission without therapeutic limitation	Patients in cancer remission or recently diagnosed with cancer, with a good life expectancy. Patients in good general condition with possible curative treatments.
Futile or unethical admission	Patients in palliative care. Patients with progressive oncological disease without further treatment options. Patients with pre-existing poor general condition. Patients refusing intensive care.
Cases to be discussed	Patients with advanced disease who may still benefit from oncological treatments and require: • ICU admission for a specific procedure with rapidly reversible pathology • Time-limited ICU trial.
Exceptional cases	Patients with very poor general condition due to onco-hematological disease that can be rapidly improved by anticancer therapy (*e.g.*, tumour-related superior cava syndrome, paraneoplastic hypercalcemia).

KEY MESSAGES FOR CLINICAL PRACTICE

1. **5 to 10% of onco-haematology patients are admitted to ICU within the first two years 40 following cancer diagnosis**

2. **Three types of admission to the ICU**
   - Planned admission (*e.g.*: postoperative monitoring)
   - Unplanned admission (*e.g.*: sepsis)
   - Admission revealing the presence of cancer (*i.e.*: seizure caused by brain 5 metastases)

3. **ICU-survival is similar between oncological and non-oncological populations when no more than two vital organs are affected**

4. **ECOG performance status and SAPS II score are important predictive factors of mortality among severely ill oncological patients.**

5. **Consideration of the overall health condition, the prognosis of the underlying tumour, the severity of the acute disease and the patients' preferences allow to distinguish patients that should or should not be admitted to the ICU. A time-limited ICU trial is an emerging concept to consider in uncertain case : treatment goals are established along with a predefined timeframe for their achievement.**

6. **Short-term prognosis is more closely related to the acute pathology rather than the underlying active tumour in selected patients.**

7. **Open discussions with patients and their families at cancer diagnosis and during treatment courses are mandatory for informed choice-making during an acute event.**

Figure 2 summarises these key messages.

Thus, providing them with comprehensive information and support is essential. Their involvement is invaluable in decision-making regarding potential care limitations during severe acute events. Finally, interdisciplinary collaboration is mandatory. Oncologists possess detailed knowledge of the patient's medical history, personal preferences, cancer characteristics, and treatment-related complications. But it is important to recognise that even in cases of cancer in remission, certain acute pathologies may have such poor prognoses that ICU admission benefits may be questioned. Intensivists are

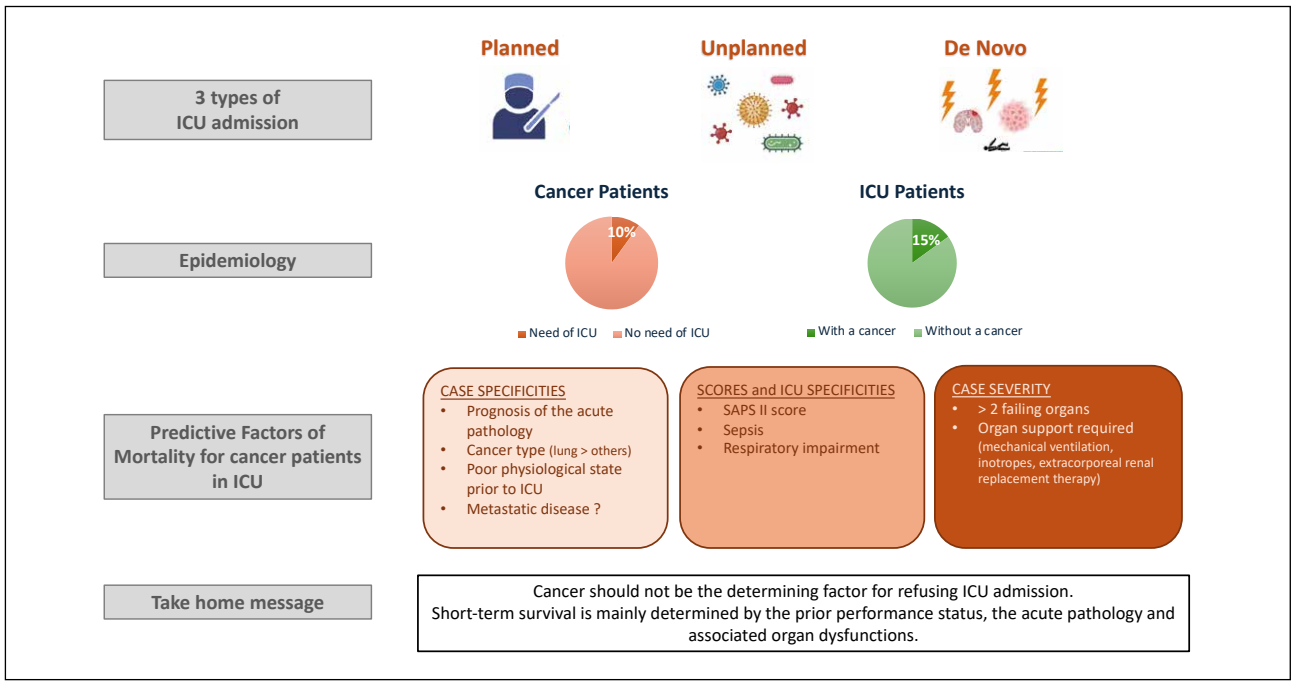

FIGURE 2. Summarises these key messages.

experts in managing acute pathologies that necessitate ICU admission, along with their prognoses. Similarly, interdisciplinary collaboration and meetings (even informal ones) bringing together various healthcare professionals (intensivists, oncologists, palliative care teams, physiotherapists, nurses, psychologists, dieticians, *etc.*) are essential for comprehensive, personalised, and thoughtful care to patients with complex diseases like cancer.[17]

CONCLUSION

In conclusion, the decision to admit cancer patients to the ICU is a multifaceted challenge, encompassing epidemiological considerations, outcomes assessment, and ethical deliberations. While historical data depicted high mortality rates among these patients, advancements in anticancer therapies and critical care management have notably improved outcomes. Various scenarios, including planned or unplanned admissions, underscore the complexity of ICU care for oncological patients. Despite challenges, studies reveal that short- and medium-term outcomes are highly influenced by the overall health condition, the severity of the acute pathology, and not only the presence of an active cancer. However, ensuring optimal patient-centred care necessitates interdisciplinary collaboration, informed discussions with patients and their families, and clear criteria for ICU admission. Further research, particularly regarding the utility of the "ICU trial" approach and the impact of ICU stays on the continuation of oncological treatments, is warranted to enhance decision-making and improve outcomes and quality of life for this vulnerable population.

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