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Invasive Mechanical Ventilation (IMV) in Cancer Patients - Long Term Follow-up and Clinical Outcomes

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Abstract

Background: Recent developments in oncology have caused a positive shift both in prognosis and quality of life for patients with solid malignancies. In the past the concept of "futility" was generally accepted regarding invasive procedure including intubation and mechanical ventilation. This concept has been challenged in recent years; however, very little long term survival outcomes have been published.

Methods: We identified patients with solid tumors who underwent Invasive Mechanical Ventilation (IMV) and were admitted to the Intensive Care Unit (ICU), treated at our institution between 2016-2020 using the institutional Electronic Medical Record System. We report clinical indications for IMV, clinical and laboratory parameters as well as long term survival outcomes.

Results: We identified a total of 46 patients who fit these criteria. We then divided the cohort to patients who died while on IMV and patients who underwent successful extubation. Indication for IMV, clinical and laboratory parameters were not found to be statistically significant in predicting outcome, except positive blood cultures (bacteremia). The average overall survival of patients successfully extubated was 66 days, with a subgroup of long-term survivors in whom median survival was 176 days.

Conclusion: We performed a retrospective analysis of cancer patients undergoing IMV and report long term survival in the group of patients who were successfully extubated. We were unable to identify prognostic markers that could help identify patients who may benefit most. We conclude that in a selected group of patients, intensive care and mechanical ventilation is both appropriate and necessary. We propose that the most important determinant for long term survival is the indication for IMV. Patients who suffered an acute insult not necessarily related to cancer progression, fared best. Clinical prudence is required in selecting these patients.

Keywords: End of life care; Solid tumors; Invasive mechanical ventilation; Cancer survivorship

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Introduction

In recent years, the notion of futility of intensive and invasive treatment of critically ill oncological patients has been challenged, including Intensive Care Unit (ICU) admission and intubation for Invasive Mechanical Ventilation (IMV). This is particularly true due to the remarkable advances in oncological treatments resulting in historically unprecedented survival, and increasingly favorable prognosis among subgroups of patients with solid tumors [1-3].

The main goal of oncology care in patients with metastatic disease is palliation: Prolongation of life, managing symptoms, improving quality of life and the relief of suffering [4]. Moreover, performing invasive procedures and providing aggressive treatments are considered a negative outcome in End-of-Life treatment [5]. Historically, the concept of futility was used to guide practitioner's decision making in critically ill cancer patients, especially relating to invasive procedures or procedures with a high cost and where resources are limited (e.g., ICU admission) [6]. The significant improvement in both overall survival and quality of life due to the advancement

in targeted treatment, immunotherapy and radiation techniques require oncologists to reconsider this dogma [2,7-9]. This exciting new reality presents a challenge for the patients, their families and the treating physicians, when considering aggressive or invasive treatments [3,6,10].

Mechanical ventilatory support is one of the common medical procedures for unstable patients due to sepsis, respiratory failure, hemodynamic instability, and other medical emergencies, all are frequent situations in oncological patients. Nevertheless, historically, it was unclear whether using IMV as a treatment option in oncological patients has an actual clinical benefit [10]. The use of IMV in oncological patients with advanced disease raises not only the question of clinical benefit but also of psycho-social issues [11]. When invasive treatments, such as IMV, are unsuccessful significant suffering of both the patient and family is often the outcome. Additionally, death under sedation and mechanical ventilation in the ICU can be extremely traumatic for the patient's family [12]. When invasive treatments, such as IMV, are unsuccessful, significant suffering of both the patient and family may result. There is paucity of data regarding long-term survival outcomes of oncological patients who underwent intubation for IMV [3,13]. In Israel, "terminal extubation" in terminal or futile cases is not permitted. Therefore, in this study, the term "extubation" refers to situations where mechanical ventilation could be safely withdrawn. However, this in itself may not be the most significant outcome for these patients. We therefore also looked at patient discharge and long-term survival.

Our aim was to evaluate factors associated with successful extubation in oncological patients with solid organ tumor and assess long term outcomes in these patients.

Methods

After institutional review board approval (HMO-0245-22), we conducted a retrospective study evaluating oncological patients who required IMV. Included in the study were all patients 18 years and above with a solid organ tumor, who were intubated and admitted to intensive care units of the Hadassah Hebrew University Medical Center between the years 2016-2020.

Data were collected from the Hadassah Electronic Medical Records. For all included cases, the following data were retrieved: Demographic information, oncological diagnosis, disease stage (early or advanced), indication for intubation as recorded in the medical file, laboratory results during hospitalization, positive blood cultures results, requirement for packed red cell infusion, number of days on invasive mechanical ventilatory support, extubation success and survival duration of extubated patients. Clinical parameters included liver function (AST, ALT or Bilirubin above upper normal limit), renal function: Creatinine (above upper normal limit), leukocytosis (above upper normal limit), acidemia (pH below lower limit).

We defined sepsis using the criteria specified in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in which sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [14]. Respiratory failure was defined as any respiratory condition requiring the institution of IMV.

Evaluated outcomes

All included patients were stratified into two groups, according to their outcome in the ICU: Patients who were successfully weaned from mechanical ventilation (successful extubation group), *vs.* patients who died ventilated (failed extubation group). Differences between these two groups of patients were evaluated.

In the successful extubation group, we further defined 'long term survivors' as patients who lived longer than 90 days post extubation. Factors associated with long term survival were evaluated.

Statistical analysis

Values are presented as medians with Interquartile Range (IQR) for continuous variables, and percentages for nominal variables. Variables associated with successful extubation and long-term survival were evaluated using the Mann-Whitney U test for continuous variables and Fisher exact tests for categorical variables, as appropriate. A multivariate logistic regression model was used to assess clinical variables associated with successful extubation correcting for age, gender and disease stage. The statistical analysis was performed using Stata version 15 (StataCorp, TX, USA), with p values <0.05 considered statistically significant.

Results

Patient characteristics

Forty-six patients were included in the study, 52% female, with a median age at admission of 65.5 years (56 to 72 years, Interquartile Range (IQR)). Patient characteristics at the time of intubation are presented in Table 1. When comparing demographic and baseline oncological disease characteristics, we found no significant differences between the two groups of patients (Table 1). Neither patient age nor an advanced oncological disease was associated with failure of successful extubation.

Indication for ICU admission and mechanical ventilation

The most common indications for intubation and ICU admission

Table 1: Patient characteristics of oncological patients who underwent Invasive Mechanical Ventilation (IMV).

	Successful extubation group n=16	Failed extubation group n=30	p-value
Age (years)	68 (62-72)	65 (54-72)	0.587
Gender, female (%)	8 (50%)	16 (53%)	1.0
Stage, advanced (%)	13 (81%)	27 (90%)	0.325
Oncological diagnosis			
Lung n (%)	1 (7%)	6 (20%)	0.438
Breast n (%)	2 (15%)	2 (6%)	
GI n (%)	8 (57%)	8 (27%)	
Bladder n (%)	-	2 (7%)	
Head and neck n (%)	-	2 (7%)	
Renal n (%)	-	3 (10%)	
Ovary n (%)	1 (7%)	3 (10%)	
Other n (%)	2 (15%)	4 (13%)	
Prior lines of oncological therapy			
0	3	6	0.41
1	5	14	
2	4	5	
3>	4	5	

GI: Including colon, esophagus, pancreas, cholangiocarcinoma; GIST: Other-melanoma, neuroendocrine tumor, unknown origin, choriocarcinoma. Prior lines of oncological therapy refer to all systemic therapies including endocrine, immunotherapy, chemotherapy, and small molecules

Table 2: Clinical indications and parameters for IMV and survival outcomes.

	Successful extubation group n=16	Failed extubation group n=30	p-value
Time to intubation (days)	5.5 (1-29)	2.5 (0-7)	0.058
ICU indication			
Respiratory n (%)	6 (37%)	8 (36%)	
Sepsis n (%)	-	14 (46%)	
GI perforation n (%)	1 (6%)	-	
Bleeding n (%)	3 (18%)	4 (13%)	
Bowel obstruction n (%)	3 (18%)	2 (6%)	0.003
Neurological n (%)	-	2 (6%)	
Anaphylaxis n (%)	1 (6%)	-	
Cardiology n (%)	1 (6%)	-	
Electrolytes n (%)	1 (6%)	-	
Duration of intubation (days)	7.5 (3.5-12)	9.5 (4-19)	0.502
Survival after extubation (days)	66 (9-142)	NS	
% Hospital discharge	68% (11)	NS	
Leukocytosis n (%)	7 (43%)	16 (53%)	0.758
PC n (%)	4 (25%)	12 (40%)	0.75
Creatinine n (%)	9 (56%)	16 (56%)	1
Liver enzymes	3 (18%)	11 (36%)	0.179
Blood cultures	9 (56%)	6 (20%)	**0.021**
Acidosis	10 (62%)	16 (53)	0.756

ICU: Intensive Care Unit; PC: Packed Cells

were respiratory failure, sepsis, bowel obstruction and gastrointestinal hemorrhage (Table 2). There was a statistically significant difference between the two groups of patients in their initial indication for ICU admission and intubation (p=0.003). All patients whose indication for intubation was sepsis, failed to reach a successful extubation and died during their ICU stay (Table 2). Whereas 56% of patients who were successfully extubated, had a reversible cause (other than sepsis) as their initial indication for intubation (acute gastrointestinal hemorrhage, bowel obstruction and perforation and anaphylaxis after chemotherapy) *vs.* 20% in the failed extubation group (p=0.021). The occurrence of respiratory failure as an indication for intubation was similar between the two groups of patients (p=0.512). The median time from hospital admission to ICU admission and intubation was 5.5 days (IQR: 1.5-27 days) in the successful extubation group and 2 days (IQR: 1-7 days) in the failed extubation group, p=0.058.

Clinical parameters during ICU admission

In most of the evaluated clinical parameters during the ICU admission, there were no statistically significant differences between the two patient groups (Table 2). Neither acidosis nor kidney or liver dysfunction were associated with failed extubation. However, patients in the successful extubation group were more likely to have a blood culture positive for a bacterial pathogen when compared to the failed extubation group (56% in the successful group *vs.* 20% in the failed extubation group. P=0.021). Additional clinical parameters assessed during ICU admission are presented in Table 2.

Multivariate analysis

Multivariate analysis, corrected for age, gender, disease stage and number of prior chemotherapy treatments, showed that independent predictors of extubation success were a reversible cause for intubation (odds ratio: 17.1 95% CI 1.8-164.7, p=0.014), blood cultures positive for a bacterial pathogen (odds ratio: 13.6 95% CI 1.4-130.6, p=0.024) and number of days from hospital admission to ICU admission and intubation (odds ratio: 1.1 95% CI 1.0-1.3 per day, p=0.033).

Long term outcome/outcome following a successful extubation

Overall, the median time on IMV was 8.5 days (IQR: 4-19 days), this was similar between the two patient groups. The median survival, after extubation, for patients in the successful extubation group was 66 days (IQR: 9-142 days). Six patients survived more than 90 days, post extubation. These patients were considered long term survivors. The median survival time in these six patients was 174 days (IQR: 129-360 days). All long-term survivors had a gastrointestinal malignancy as their primary oncological diagnosis (p=0.011). No other variable predicted long-term survival in patients who were successfully extubated.

Discussion

In this observational retrospective study, we evaluated factors associated with successful extubation after ICU admission and mechanical ventilation in oncological patients with solid organ tumors. We show that a significant number of patients may benefit from aggressive management with mechanical ventilation despite suffering from advanced metastatic disease. Our results show that patients with a reversible cause for intubation and mechanical ventilation are significantly more likely to survive their ICU admission, independent of age, disease stage and prior lines of chemotherapy.

A meta-analysis including 22 studies on oncological patients' prognosis in the ICU on mechanical ventilation found that the ICU survival rate was 34% although in-hospital mortality was 87% and 6-month survival was only 6.8% [15]. Nevertheless, the authors concluded that intubation should be considered when appropriate. The main limitation of this review was the heterogeneity of the population including patients with hematological, bone marrow transplantation and solid tumor malignancies-diverse diseases each with its own unique prognosis. Additionally, many of these studies are dated and do not include modern oncological treatments which significantly change the prognosis in these cases. Few trials reported solely on patients with solid malignancies in the modern treatment era. One such study by Sihn et al. reported 28th day mortality rate in intubated patients stratified to lung cancer patients and other solid malignancies as well as local or metastatic disease. They report a 28-day mortality of 44.2% to 66.2% with non-metastatic non-lung cancer with the lowest mortality rate and metastatic lung cancer [13]. However, long term data past 28 days was not available. Revon-Riviere, Pauly et al. identified young patients most likely to undergo invasive care among patients who die in the hospital and identified factors most likely to influence the practitioner's decision, including prior lines of therapy, solid *vs.* hematological tumors and age, however outcome was similar [16].

Indeed, taken together; the increase in cancer patient's survival and improvement in critical care in the last decade there is a need for re-evaluation of the role of IMV in this setting. As early as 2015 Ñamendys-Silva et al. [6], suggested the concept of "futility" of intensive care in oncological patients outdated and inappropriate nowadays. They conclude with suggestions as to which oncological patients may benefit from intensive care [6].

In this study we describe a cohort of cancer patients who

underwent intubation and intensive treatment in the ICU.

The patients who seemed to benefit the most as defined by the longest survival had acute reversible emergencies such as acute bleeding, bowel obstruction or perforation and anaphylaxis. This suggests that the best candidates for intensive treatment are patients with acute reversible insults indirectly related to their oncological diagnosis. Alternatively, patients with sepsis had the least favorable prognosis with no patient with sepsis successfully extubated. Patients intubated for respiratory failure were extubated in 42% (6/14) cases possibly representing the heterogeneous etiology of respiratory failure. This suggests that prudent clinical judgment is required when deciding to intubate patients with respiratory failure. For example, a patient with progressive lung metastasis or lymphangitic carcinomatosis may not benefit, while reversible conditions such as pneumonia or pneumonitis may benefit.

We found no prognostic factors in demographic characteristics such as age, gender, previous lines of therapy and successful extubation. We also were unable to show prognostic significance of laboratory parameters representing organ failure.

The shared decision between practitioner, patient and family members for intensive and invasive end of life care is extremely multifaceted and complicated. Our study is undeniably influenced by the unique cultural and religious context of practicing in Israel in general and Jerusalem specifically. The majority of both the Israeli Jewish and Muslim population identify themselves as religiously motivated in issues related to death [17,18]. This, trend may influence the patient's and family's preference. Whereas, intubation and mechanical ventilation as a means of life prolongation often is religiously and culturally motivated, discontinuation of mechanical ventilation once preformed is not a legal option in Israel [19]. These issues both warrant further study and introduce bias into our cohort. Indeed, a similar study from a single institution in Korea showed a trend towards less intensive care, possibly due to the above mentioned cultural and religious considerations [20].

Another significant limitation of our study is its retrospective observational nature as well as the small cohort size. Despite these limitations, we show a significant number of patients who benefited from IMV in our institution.

Conclusion

We concur with the recent literature that the notion that metastatic patients are not ideal candidates for intensive and invasive procedures should be revisited. This is especially true in the modern oncological landscape which includes revolutionary new treatments that caused a paradigm shift in the overall survival and quality of life of many oncological patients. There is however very little data published or known regarding prognostic factors which may help guide these critical decisions. While we have shown that some patients may have long term benefit from intubation, we also recognize the need to identify patients in whom intubation is unlikely to benefit the patient. Limited financial and human resources required for IMV and ICU admission may not be justified if the treatment is considered futile. All these factors: Medical and oncological-prognostic, financial, religious, and cultural considerations make the decision for mechanical ventilation extremely multifaceted and difficult both for the oncologist, intensivist and the patients and their family. We recommend IMV and ICU admission for those oncology patients with acute reversible disease processes.

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