



# Outcome of invasive mechanical ventilation in cancer patients: Intubate or not to intubate a patient with cancer

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## ABSTRACT

**Purpose:** The outcome of cancer patients who undergo mechanical ventilation has been grim. However, it has lately become more promising, creating hesitation when approaching the decision to intubate a cancer patient. Therefore, the main goal was to find some factors that could predict mortality.

**Material and methods:** Studies were selected on the basis of their information wholeness, the year done, patients' number, participating country, underlying hematological or nonhematological malignancies, ventilation duration, ICU survival, hospital survival, long term survival, disease activity, and other contributing factors.

**Results:** Twenty-two studies were included which accrued 3115 patients. The average ICU survival was 32.4%, and long-term survival was 10.2%. Over the years, the outcome of cancer patients undergoing mechanical ventilation has improved. The most important predicting factors are: The respiratory failure etiology, the performance status, the disease activity, and the SOFA score.

**Conclusions:** The aforementioned predicting factors could be used when approaching the decision to intubate. When in doubt, we should give the benefit to the patient, proceed to intubate and reevaluate progress daily and in doing so, we would suggest to use the trends in SOFA score and weaning index to assess success or failure of invasive mechanical ventilation.

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## 1. Introduction

Lately, there has been significant progress in the management of neoplastic diseases. New chemotherapeutic agents, targeted therapies to downregulate cancer growth, new ventilatory strategies, improvement in pharmaceutical and technological supports, and perhaps a better selection of patients, have made this process a *bonafede* reality [37]. However, these therapies and techniques have rendered severely affected patients with marked immunological impairment and prone to develop organ/system failure, particularly respiratory failure. It is estimated that 40% of patients will suffer from respiratory failure and although the survival of cancer patients undergoing invasive mechanical ventilation (IMV) has improved Fig. 1, for some cancer patients, the institution of IMV is just an exercise of medical futility and prolongation of suffering. Consequently, it is imperative to improve the accuracy to predict who will benefit from IMV [8].

The management of respiratory failure is focused in the therapy of the underlying cause, e.g. infection, hemorrhage, pulmonary edema, pneumonitis from drugs or other inhalational injuries, or neoplastic

involvement; and in providing optimal oxygenation and adequate ventilation. However, when the patient is unable to keep up with the gas exchange demands, and does not benefit from non-invasive ventilator support, then it is conventional to intubate and institute IMV [15].

The institution of IMV implies a complete dependence to an artificial device, which brings complications, such as infections, barotrauma, hemodynamic instability, oxygen toxicity, overdistention-related lung injury, etc. Consequently, the consensus is that, unless IMV is used for a short period of time, the outcome of patients who required IMV is dubious. Contrarily some malignant neoplasms are also considered incurable conditions, with high mortality rates.

Consequently, it has been hypothesized that when the need for IMV ensues in a cancer patient, it creates a situation of uncertainty, that the decision to use any medical therapeutic intervention becomes difficult [31].

Therefore, we have conducted a systematic literature review to summarize the world experience to attempt to establish a consensus that may help the clinician in this difficult task Fig. 1.

## 2. Methods

A computerized literature search was performed using the Text Search Database linkage to the National Library of Medicine in Medline

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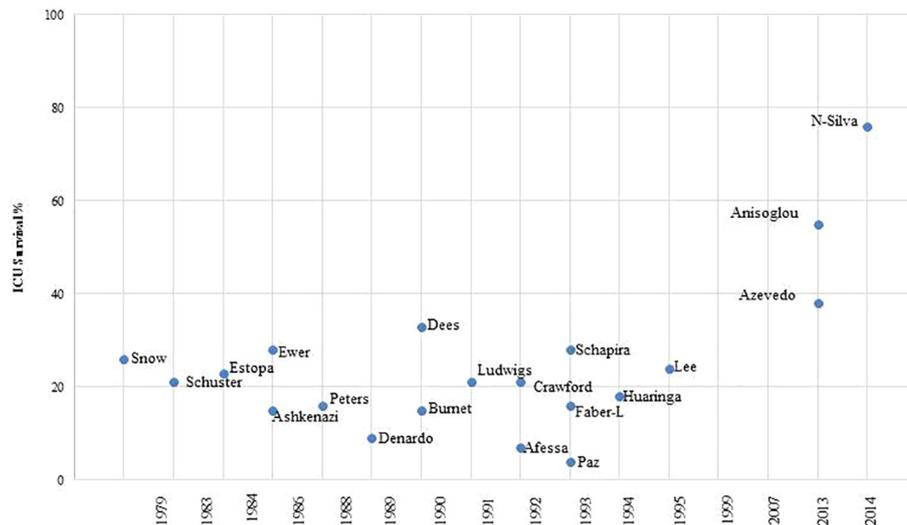


Fig. 1. ICU survival trend over last 40 year

and Cancer lit from 1965 to present, and the entire Current Concepts Database, matching the items: “outcome”, “mechanical ventilation”, “cancer patients”, “malignant neoplasms,” and “hematological malignancies.”

A systematic review was then performed following the PRISMA guidelines. Twenty-two studies were selected on the basis of the availability of information about outcome, use of invasive mechanical ventilation, and predictors of survival or mortality.

### 3. Results

Twenty-two studies were selected. They are summarized in chronological order in Tables 1 and 2.

**Table 1**  
Outcome of mechanical ventilation in cancer patients.

Author	# patients	Year	Place	Hemat. Neopl.	Other cancers	Mech. Vent. duration
Snow	180	1979	USA	N/R	N/R	N/R
Schuster	52	1983	USA	Yes	N/R	5 Days
Estopa	26	1984	SPAIN	N/R	N/R	N/R
Ewer	46	1986	USA	No	Lung	6 Days
Ashkenazi	18	1986	USA	N/R	N/R	N/R
Peters	116	1988	USA	Yes	N/R	N/R
Denard	44	1989	USA	BMT	N/R	5 Days
Brunet	111	1990	France	Yes	N/R	N/R
Dees	49	1990	Netherlands	N/R	N/R	N/R
Ludwigs	38	1991	Sweden	Yes	Yes	4.7 Days
Crawford	348	1992	USA	BMT	N/R	8 days
Afessa	27	1992	USA	BMT	N/R	N/R
Paz	28	1993	USA	BMT	N/R	N/R
Faber-L	191	1993	USA	Yes	N/R	N/R
Schapira	54	1993	USA	Yes	Solid tumors	N/R
Huaringa	61	1994	USA	BMT	Breast BMT	15 Days
Lee	115	1995	China	Yes	Yes	N/R
Groeger	782	1999	USA	BMT	Solid tumors	N/R
Azoulay	188	2007	France	Yes	Lung/Breast	5 days
Azevedo	178	2013	Brazil	Yes	Solid Tumor	5 Days
Anisoglou	105	2013	Greece	No	Lung Cancer	N/R
N - Silva	358	2014	Mexico	Yes	Solid tumors	4 days

BMT: Bone marrow transplantation.

The first study was conducted by Snow [35] et al. at the M.D. Anderson Cancer Center, who reviewed 180 cancer patients requiring IMV and reported a 74% intensive care unit (ICU) mortality, and 13% and 7% survival in 2 and 6 months respectively. These investigators noted a correlation between mortality and the number of organ systems with major dysfunction. Thrombocytopenia was the most significant factor to correlate with mortality.

Schuster [33] et al. published the Barnes Hospital experience, reporting 77 patients with hematological malignancies admitted to the MICU over a 21-month period, and found that only 4 out of 52 patients, who required IMV, survived. All four survivors used IMV for a short time (< 5 days) and had noninfectious etiologies for their respiratory failure. They concluded that the use of IMV, unless it is needed for a short time, constitutes a harbinger of a grim prognosis [32].

The first study in Europe was conducted by Estopa [14] et al., who reviewed the cases of 30 patients with hematological malignancies, who were admitted to the MICU. Twenty-six of them required IMV, with a 77% ICU mortality and 92% in-hospital mortality. Only 2 of the patients were discharged home and no significant predicting factors were reported.

Subsequently, Ewer [13] et al. analyzed the outcome of 46 lung cancer patients at M.D. Anderson Cancer Center who required IMV and reported an ICU mortality of 85% and a hospital mortality of 91%. The duration of IMV was the only discriminatory factor between survivors and non-survivors, because all patients who were successfully weaned required IMV for less than six days.

Ashkenazi [4] et al. reported 29 patients admitted to the ICU at the Shands Hospital, 18 required IMV. The ICU mortality in this 18 IMV-requiring group was 72% and the 2-month survival was 22%. The factors that predicted survival were: Age < 35, Disease stage, Acute Physiological score, and the coexistence of pneumonia.

Peters [29] et al. reported 116 patients with hematological malignancies requiring IMV at the Mayo Clinic, during a ten-year period, and observed 84% in-hospital mortality. These investigators found that age, neutrophil count, ICU length of stay, and IMV duration were not discriminatory factors between survivors and non-survivors. However, the highest survival rate was observed in patients with chronic lymphocytic leukemia (42%).

Denardo [12] et al. studied 50 bone marrow transplant (BMT) recipients, 44 of whom, required IMV and noted a 91% ICU mortality and 0% survival in those who needed IMV > 5 days. These investigators raised the issue of medical futility, inquiring early information to the patients and relatives about prognostic estimates.

**Table 2**  
Survival rates and other factors determining outcome in cancer patients requiring mechanical ventilation.

	ICU survival %	Hospital survival %	Long term survival	Disease activity	Mortality predicting factors
Snow	26%	13%	6 mo. 7%	Yes	MSOF, thrombocytopenia
Schuster	21%	8%	N/R	Yes	CRH
Estopa	23%	8%	N/R	Yes	CMV, DAH
Ewer	15%	9%	N/R	Yes	Direct airway involvement by CA
Ashkenazi	28%	22%	2 mo. 22%	Yes	Pneumonia
Peters	16%	16%	N/R	No	N/R
Denard	9%	N/R	N/R	N/R	N/R
Brunet	15%	15%	N/R	N/R	Dialysis
Dees	33%	26%	N/R	N/R	Apache II score
Ludwigs	21%	21%	N/R	N/R	Pneumonia
Crawford	21%	4%	6 mo. 3%	Yes	HLA Comp
Afessa	7%	7%	N/R	N/R	Pneumonia, MSOF
Paz	4%	N/R	N/R	No	Apache II score
Faber-L	16%	6%	6 mo. 3%	No	Age, Timing of intubation
Schapiro	28%	28%	6 mo. 16%	Yes	N/R
Huaringa	18%	18%	6 mo. 5%	Yes	Pneumonia, GVHD, Aspergillosis
Lee	24%	8%	3 mo. 3%	N/R	
Groeger	N/R	24%	N/R	Yes	Intub. After 24 h, leukemia, DIC, Arrhythmias, Vasopressor therapy
Azoulay	N/R	22%	N/R	Yes	COPD, HTN, CHF
Azevedo	38%	27%	N/R	yes	Performance status, COPD, Dialysis, Vasopressors
Anisoglou	55%	44%	6 mo. 23%	Yes	Performance status, sepsis, vasopressors, thrombocytopenia
N - Silva	76%	N/R	N/R	N/R	ARDS

MSOF: Multisystem organ failure, CRH: Chronic refractory hypotension, CMV: Cytomegalovirus, DAH Diffuse alveolar hemorrhage, HLA: Human leukocyte antigen, GVHD: Graft vs. host disease, DIC: Disseminated intravascular coagulation, N/R: Not reported. Numbers were rounded to the nearest whole numbers to facilitate comparison between studies.

Brunet [7] et al. reported 260 patients with hematological malignancies admitted to the MICU, and found an in-hospital mortality of 85% in the 111 patients who required IMV, claiming that prolonged IMV in these patients may still offer long-term survival, but clarifying that the associated concomitant use of IMV and hemodialysis constitute poor prognosis indexes.

Dees [11] et al. analyzed 49 medically treated cancer patients who underwent IMV, and observed 67% ICU mortality and 76% in-hospital mortality. They concluded that the Apache II score was strongly associated with outcome after IMV.

Ludwigs [24] et al. reported 1008 admissions to the MICU of patients who required IMV, however, only 38 of them were cancer patients. In this group, these investigators reported a 79% ICU mortality, and stated discouraging conclusions, demanding improvements in quality of monitoring systems.

Crawford [10] et al. reported 348 BMT patients at the Fred Hutchison Cancer Research Center, and found that older age (defined as >20 years), active malignancy and donor-recipient marrow HLA non-identity were risk factors for IMV need. Of the 348 patients, 276 died in the ICU (79% mortality), only 15 were discharged from the hospital (4% survival rate) and the 6-month survival rate was only 3%. They recommended that emphasis be made on counseling patients and relatives regarding this treatment [9].

Afessa [1] et al. studied 27 BMT patients who required IMV, and reported 93% ICU mortality. No significant differences were found in age, sex, BMT type, graft vs. host disease (GVHD), conditioning regimen, ICU length of stay, and Apache II score, between survivors and non-survivors.

Paz [28] et al. reported BMT patients who were admitted to the MICU and found that IMV was a predictor of mortality, because only 1 out of 28 IMV patients survived. They found a correlation between the Apache II score and mortality rate.

Faber-Langendoen [15] et al. reported 653 BMT patients. Of the 653, 191 required IMV, and of these, only 30 (15.7%) survived to be extubated, only 18 were alive one week after extubation, and only 6 patients (3%) were alive 6 months after. Age was an important factor for survival because from the group of patients older than 40 years of age, 98% died, and the other influencing factor was the timing of intubation, due to the fact that of those intubated within 90 days of transplant, 94% died, raising the issue of medical futility.

Schapiro [34] et al. reported the experience at Moffitt Cancer Center, where they noted that the survival of patients requiring IMV (27.8%) was significantly lower than the one of those who did not require IMV (72.4%). They indicated that leukemic patients who required IMV had the poorest prognosis. Of those patients who required IMV longer than 13 days, none of them survived.

Once again at M.D. Anderson Cancer Center, Huaringa [20] et al. (1994) reported 61 BMT patients who required IMV, and found 82% ICU mortality and a 4.8% 6-month survival. In this study, numerous factors failed to predict mortality; but, it was evident that whereas GVHD was a predictor of bad outcome, noninfectious complications such as pulmonary edema as etiology of the respiratory failure was indeed a predictor of good outcome.

Lee [23] et al. studied 115 patients with solid tumors and hematological malignancies, who used IMV, and reported a 77% ICU mortality, 92% in-hospital mortality and 3% 3-month survival. They did not find any significant mortality predicting factors, but emphasized the tremendous economic impact the care of these patients yielded, and concluded that IMV should not be routinely used in cancer patients.

Groeger [19] et al. performed a prospective multicenter observational study in 5 academic tertiary care centers, and analyzed 782 cancer patients, who received IMV, and concluded in seven variables associated with increased mortality: Need for intubation after being 24 h in the ICU, leukemia, progression or recurrence of cancer, allogeneic BMT, cardiac arrhythmias, disseminated intravascular coagulation, and vasopressor therapy. Prior surgery with curative intent was a good survival predictor. The overall hospital mortality was 76%.

Azoulay [5] et al. studied 188 who required IMV, and found that 103 survived the first 4 ICU days, but thereafter he observed that the hospital survival was only 21.8%. Because of the significant difference between the initial 4-day survival and the actual hospital survival, the authors suggested a reappraisal of the philosophy of care on ICU day 5.

Azevedo [3] et al. conducted a secondary analysis of a prospective cohort in 28 patients with cancer requiring IMV and found that hospital survival was predicted by good performance status, lack of progression of the underlying malignancy and lack of tumor airway involvement.

Anisoglou [2] et al. conducted a retrospective analysis of 105 lung cancer patients who required IMV and found that the most significant factors predicting poor outcome upon admission were Apache II and SOFA scores, performance status, vasopressor use, length of mechanical ventilation duration, and, thrombocytopenia.

Namendys-Silva [25] described 358 cancer patients who required IMV, with a median ICU stay of 4 days. The ICU mortality in these patients was 73% in hematological malignancies and 34% in solid tumors. He indicated that the severity of respiratory failure could be the main predictor of outcome in these patients, as expressed in the mortality trend progression in ARDS as the condition advances from mild (27% mortality), moderate (32% mortality), and severe ARDS (45% mortality).

#### 4. Discussion

It has been known since the study of Zwillich [38] et al. that IMV brings many complications. Indeed IMV constitutes a harbinger of high mortality rate, even when dealing with a non-cancer patient population.

Cancer patients are even more susceptible to complications because they are immunosuppressed, due to chemotherapy or the nature of the underlying neoplasia. Poe et al [30], in a review of 99 immunocompromised patients, identified 3 predicting factors for mortality, and those were hypoxemia, use of corticosteroids, and IMV.

Eleven of 22 studies about outcome of IMV in cancer patients, expressed conclusions discouraging the use of IMV, three were in favor of its use, and one adopted neutral position.

As depicted in Table 1, most of the studies were done in USA [13], but 6 were undertaken in Europe (2 in France, one in Spain, Netherlands, Greece, and Sweden), 2 were performed in Latin America (Brazil and Mexico) and one in Asia (China).

Considering all mechanically ventilated cancer patients reported in these studies, the total accrual was 3115 with an average ICU mortality rate of 67.6%.

The average IMV duration, considering the 6 studies that reported this factor was 7.3 days. The average in-hospital mortality rate, counting on the 12 studies that reported it, was 87%. Seven studies documented long-term survival: Snow et al. revealed a 7% 6-month survival, Ashkenazi et al. disclosed 22% 2-month survival, Crawford et al. reported a 3% 6-month survival as did Faber-Langendoen et al., Huaringa et al. observed 4.8% 6-month survival, and Lee et al. reported 3% 3-month survival. The average 6-month survival was 6.8%.

The factors that influenced the outcome of cancer patients undergoing IMV were:

- 1) Age, found to be predictor of mortality in the studies of Ashkenazi et al. and Crawford et al.
- 2) The performance status was also encountered to be strong predictor of mortality with Zubrod [27] scores 3 to 4 (which corresponds to Karnofsky 10–50) having very high predictive value for mortality.
- 3) Disease activity and advanced stage were also reported to be strong predictors of bad outcome in the aforementioned reviews.
- 4) The length of IMV [18] was reported as discriminatory factor in the studies of Schuster et al, Dees et al, Huaringa et al., and Schapira et al.: The shorter the length the better the survival [17].
- 5) Multisystem organ failure probably affected outcome in all studies, but it was mentioned as mortality predictor only in the studies of Snow et al and Afessa et al. However, the APACHE II score was found to be a good correlation with outcome in 3 studies: The one of Ashkenazi et al., Dees et al., and Paz et al. The SOFA (Sequential Organ Failure Assessment) score [16] was found to correlate with mortality in the study performed by Azevedo et al. Because out of maximum of 24 points, it has been well established by Vincent [39] et al. and others, that a SOFA score >15 predicts >90% of ICU mortality.
- 6) Infection, as etiology of the respiratory failure was the most frequently quoted predictor of bad outcome, as reported by Ashkenazi et al, Ludwigs et al, Afessa et al., and Huaringa et al. On the other hand, Pulmonary Edema as etiology of the respiratory failure has a reasonably good prognosis. Whereas, if the respiratory failure is

due to involvement of the respiratory system by the cancer, it is a sign of bad prognosis.

- 7) Dialysis was found to be a predictor of mortality in the study of Brunet et al.
- 8) Graft vs. Host Disease (GVHD) was found to be a predictor of bad outcome in the study of Huaringa et al.

Consequently, we have learned that it is imperative that this vital decision to intubate or not to intubate a patient with cancer who develops respiratory failure must be taken by a multidisciplinary team composed of the primary care physician, the intensivist, the oncologist, palliative care specialist, and any other specialists participating in the care of the patient, and taking into consideration all these 8 criteria [22][26].

This literature review, although somewhat limited due to the heterogeneity of the patient population and some inherent selection bias, reflects the consensus that is emanating in the Critical Care world, that whereas in one side we are going beyond our means in terms of the ever-increasing expenditures in health care, on the other hand, we are not achieving the ultimate goal, which is to restore life to our patients into decent, enjoyable standards of life. Instead, we may be prolonging not only their suffering lives but also prolonging the stress and anguish of their relatives. In many occasions, this prolongation of suffering is motivated by the patient's relatives, who might not understand the two basic ethical principles that physicians are obliged to comply, which are: The principle of beneficence: Do good to people, and the principle of nonmaleficence: Do not harm people. Prolonging suffering lives goes against the principle of nonmaleficence [6]. In addition, there is frequent misinterpretation of the Patient's Self-Determination Act [40], which states that the patient has the right to forego any therapeutic decision, but it does not state that the patient has the right to demand certain therapeutic intervention even when the physician does not consider it pertinent.

#### 5. Conclusions

- 1) The outcome of IMV in cancer patients is historically poor, but with the advances in technology, it has improved.
- 2) It is evident that we cannot generalize and apply a formula that may predict mortality in all cancer patients at all institutions; consequently, every medical institution should establish its own disease-specific outcomes.
- 3) Terms such as medical appropriateness and medical futility should be defined in every institution based on its outcome analysis; and complete disclosure should be done a priori to the patients and relatives.
- 4) When there is a doubt in the outcome prediction of the cancer patient to undergo IMV, the patient should be given the benefit of the doubt and should be intubated but the philosophy of care should be reassessed daily on the basis of the progress of the respiratory failure which could be objectivized using the SOFA score and the weaning index [21] on a daily basis.
- 5) Quality of life assessment must be performed [36], considering the patient's own perceptions and expectations; and agreement must be reached that at some point in the care of the patient, the physician's expertise and authority must prevail over the patient autonomy in order to avoid practicing medical futility and its catastrophic social, psychological and economic impact.

#### Institution where the work was done

White Memorial Medical Center.

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Dr. Francis performed the review of the literature.

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