

## REVIEW ARTICLE

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# Cardiopulmonary resuscitation in end-stage cancer patients

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### Summary

*Cardiopulmonary resuscitation (CPR) in patients with end-stage cancer is an issue of significant clinical and ethical importance. In general, the overall survival to discharge in cancer patients is referred to be 6.2% (localised - 9.5% vs. metastatic disease - 5.6%) compared to 15% of unselected in-hospital arrests. However, immediate survival, as well as survival to discharge after a successful CPR is affected by multiple factors. Type and extend of tumor, degree of clinical deteri-*

*oration, functional status and many other factors do correlate with outcome in different degrees. Critical illness scoring systems are commonly used in order to assess performance status of patients and predict outcome. This article will review all the above mentioned factors, as well as patients' perception about "do-not-resuscitate" orders and palliative care.*

**Key words:** cancer, cardiopulmonary resuscitation, "do not resuscitate" order, survival

### Introduction

Modern CPR was first introduced in 1960 for otherwise healthy subjects with a reversible condition who experienced sudden and unexpected cardiorespiratory arrest [1]. Since then, CPR has gained widespread use and it is provided routinely in all institutions and patients unless a specific order of "do not attempt resuscitation" (DNAR) has been recorded. Actually in our days, CPR is applied in almost in any patient who is dying (or is dead) independently of the underlying disease. In many cases the application of CPR prolongs the dying process through temporary restoration of cardiac function.

The success rates in the 1960s were reported to be as high as 70%, but further studies failed to prove such great success. In the 1980s, the success rate of in-hospital resuscitation was reported to be 39% and survival to discharge only 17% [2]. Recent studies, which are mostly focused on survival after resuscitation of patients with critical illness and malignancies, report lower survival rates [3] according to various parameters such as performance status, type of tumor, localized or metastatic disease and the degree of clinical deterioration (expected vs. unexpected arrest). The outcome and prognostic factors of CPR in patients with terminal illness, and particularly with end-stage cancer, bring clinical and ethical issues of

great importance [4-6]. Actually, in our days in-hospital CPR has become an integral part of the dying process worldwide with questionable reasoning and outcomes.

In this review, an effort will be made to analyse all parameters which affect survival after CPR in end-stage cancer patients, and to discuss the ethics of resuscitation based on doctors' and patients' point of view.

### Outcomes following CPR in patients with cancer

Cancer is the second cause of death in the United States and the European Union and is expected to become the leading cause within the next 10 years [3,7]. Survival in patients with cancer has been improved over time [3], but the choice between aggressive resuscitation attempts or palliative care in end-stage patients is still under ethical and clinical consideration, particularly in patients with metastatic disease.

In general, cancer was identified as a bad prognostic factor for successful resuscitation [7] after cardiac arrest and several studies tried to identify factors promising favorable outcomes.

In a meta-analysis recently published by Reisfield et al. [3], analysing 42 studies of the last 40 years (totally 1707 patients), the overall survival rate of cancer patients

to discharge from hospital was 6.2% (95% confidence interval/CI 3.2-9.1). Due to the fact that cancer is a heterogeneous group of patients, several subgroups were further analysed and presented below.

According to previous studies, survival seems to be different, depending on the type of tumor. In the meta-analysis of Reisfield et al. patients with solid tumors seem to have better outcome ( $p = 0.001$ ), since 7.1% (95% CI 3.3-10.9) were successfully resuscitated compared to 2% (95% CI 4.4) of patients with hematological malignancies [3]. Among hematological malignancies, survival of patients with lymphoma/myeloma was 3.4%, with leukaemia 0.9%, and with hematopoietic stem cell recipients (HSCT) 0.0% ( $p = 0.272$ ).

A significant difference ( $p = 0.001$ ) was also observed among patients who were resuscitated on medical or surgical wards compared to patients in the intensive care units (ICUs) (10.1 and 2.2%, respectively) [3], which possibly reflects the severity of illness and underlying/concomitant diseases in these patients and concurrent multiple organ dysfunction.

Regarding metastatic solid tumors, successful resuscitation according to previous studies was about 5.6% (95% CI 1.4-8.6) and differed significantly ( $p = 0.05$ ) compared to patients with localized-non metastatic solid tumors (9.5%; 95% CI 4.3-14.6) [3]. On the other hand, in a study by Vitelli et al. [7], a strong correlation was observed between functional (performance) status of patients and CPR outcome, suggesting that metastatic disease is not itself predictive of outcome. Also, according to Reisfield et al. [3] patients with localized and metastatic disease did not differ among those who arrested on an ICU (4.9 vs. 5.3%, respectively,  $p = 0.915$ ) or on a medical/surgical ward (19.4 vs. 16.2%, respectively,  $p = 0.736$ ), indicating that metastasis does not predict outcome of CPR.

Performance status, critical illness and clinical deterioration (expected vs. unexpected arrest) were the most important predictors of resuscitation success than the presence of metastatic disease. It has been reported that patients with a Karnofsky performance status (KPS) of  $\leq 50\%$  had a 2.3% chance of survival, whereas those with a KPS score of  $>50\%$  had a 17.5% chance of survival after CPR [8].

In addition, unexpected cardiac arrest is correlated with a higher rate of survival compared to arrests which follow a gradual deterioration (21.9 vs. 0%) [2].

Age also proved to be an independent predictor of outcome of critically ill patients aged  $> 60$  years in a study by Soares et al. [9], but also the severity of organ failure and cancer status affected mortality. However, the authors state that selected older patients with cancer can benefit from intensive care, while patients with poor functional status, more than two organ failures, severe comorbidities

and uncontrolled cancer do not.

Another issue of great importance when discussing survival is the time point which is measured. Immediate survival after a cardiopulmonary arrest differs significantly compared to survival to hospital discharge (45.4 vs. 12.6%). According to the meta-analysis of Reisfield et al., the overall percentage of survival to discharge as referred above was 6.2% (localised - 9.5% vs. metastatic disease - 5.6%) compared to 15% of unselected in-hospital arrests [3].

Similarly, about a third of the studies analysed reported immediate resuscitation success rates around 45.4% [3]. Overall survival to discharge in these studies was 5.6%, while survival to discharge for those who survived the resuscitation attempt was 12.6%. This means that when surviving initial resuscitation there is a chance of leaving the hospital 1 in 10, while 9 in 10 initial CPR survivors die in the hospital.

Finally, there is a suggestion of a trend in increasing odds of survival over time that is before 1990 compared to 1990 and thereafter (odds ratio for year 1.05; 95% CI 0.99-1.11;  $p = 0.098$ ). Better outcomes of CPR after 1990 maybe explained in part by the increasingly selective application of CPR in recent years [3], i.e. in recent years the application of CPR in cancer patient is more selectively applied according to diagnosis or prognosis compared to early 1960s, 1970s and 1980s. A 16% of DNAR has been reported in cancer deaths in the past, while an 86% of in-patients deaths had a DNAR in 2005 [10,11].

Better outcomes after 1990s may be also explained in part by the better application of the technique of CPR. According to the literature, patients receiving good quality bystander CPR may have 4-fold higher survival to hospital discharge compared to poor quality CPR [12].

We should always bear in mind that survival percentages do not include a significant number of cancer patients that did not have a CPR and thus actual survival rates and efficacy of CPR maybe overestimated. According to a recently published paper there is also a lack of data on long-term follow-up after hospital discharge, and on the other hand we should always have in mind that successful resuscitation does nothing to alter the underlying malignancy.

According to limited available data, survival after successful CPR in cancer patients is disappointing. Most of the patients die within days or weeks after hospital discharge either at home, nursing home or hospice [7,13,14].

### **Chronic health and organ failure scoring systems as predictors of survival**

Scoring systems have been developed in intensive

care medicine, in order to assess severity of illness, predict outcome of patients admitted and also assist clinical decision-making. These systems have been constructed in general ICU populations, and the question is whether they can be used as predictors regarding patients with cancer. However, most studies state that survival after a successful CPR is guided by performance status and the degree of clinical deterioration rather than the type of tumor or the presence of metastatic disease. Indeed, a study by Cornet et al. [15], dealing with survival of patients with hematological malignancies who were transferred to the ICU due to life-threatening complications of their disease, states that scoring systems such as Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS II) and Acute Physiology and Chronic Health Evaluation (APACHE II/III) can predict long-term outcome in patients with malignancies. At the time of admission to the ICU, SAPS II and SOFA scores were proved to be significantly higher to non-survivors, while SOFA score was also related to survival time. The study concludes that SOFA scoring system better predicts survival in patients with hematological malignancies compared to SAPS II and APACHE II scores, with a mean value of SOFA score of 11.2 ( $\pm$  3.5) for non-survivors vs. 6.4 ( $\pm$  3.3) for survivors. Another study by Schellongowski et al. [16], concluded that SAPS II is superior to APACHE II and ICMM (a newly developed ICU Cancer Mortality Model) in predicting mortality of patients with cancer admitted to the ICU. On the other hand, two other studies [17,18] support that neither APACHE II, SAPS II and SOFA scores are accurate enough to be used in cancer patients admitted in the ICU, because long-term mortality is influenced by other factors as well. The third version of SAPS (III) which is recently developed, was also evaluated in one study, and proved to be accurate in predicting hospital mortality in critically ill patients with cancer [19]. However, more studies are needed to prove the accuracy of illness' severity scores in predicting the outcome of critically ill patients, and to guide decisions about resuscitation and ICU admission. All authors agree that prognostic models should always be used on individual basis in decision-making concerning life-sustaining therapies and triage for ICU admission.

### Patients' point of view

It has been said that "few initials in medicine today evoke as much symbolism or controversy as the DNAR order" [20]. It is true that such an order is typically invoked for patients with critical illness, including patients with end-stage cancer, but it always requires authoriza-

tion. Patients' opinion about DNAR orders should also be considered. In a study by Olver et al. [21], most patients with end-stage cancer thought that resuscitation is the default option in every hospital and that refraining from it would be a deviation from normal hospital procedures, appropriate only when "nothing else could be done" and "all systems fail". On the other hand, over half of patients in this study did not understand the meaning of "good palliative care orders", but they were positive about it. It is very interesting that the majority of patients in the study thought that DNAR is their right to decide as autonomous adults, but also did not think of themselves as people under this situation. In another study by the same team of psychologists, referring to patients who were expected to die from cancer within 3 months, patients stated that decision making for DNAR orders is supposed to be shared between themselves and the doctors and also that this decision should be based on medical facts [20,22]. The proper timing for such a discussion revealed different opinions between early discussions and late ones, validating the difficulty stated by oncologists to choose the appropriate timing. On the other hand, patients involved in a study by Heyland et al., did not seem to have good knowledge about CPR and more than 1/3 did not wish to discuss their preferences with physicians, but preferred a conversation with the family with physician involvement [23].

These facts, based on patients' opinion, suggest that a more flexible model for DNAR orders is needed that will be able to maintain patients' autonomy and also recognize their right to choose the timing of such a discussion or not take it at all. The communication between doctors and patients must be honest and sharing in order to satisfy all parties. It is obvious that CPR and DNAR decision-making will continue to be difficult and should be guided by flexibility in order to combine different and continuously changing circumstances and patients feelings towards the end of life.

### Conclusions

Despite that initial CPR successful rates maybe as high as 45% only 1/10 of these patients have a chance to hospital discharge. Although older studies suggest that metastatic disease is associated with lower percentages of survival after CPR, it seems that other factors as well are more important in predicting outcome. Solid tumors, non-metastatic disease, unexpected arrest, hospitalization of the patient in ward, young age and performance status (i.e. KPS >50) strongly correlate with better outcomes of patients with cancer, and should be evaluated in order to guide decisions regarding the application of CPR. However, more studies are needed to assess the

prognostic value of critical illness scoring systems, because the available data are conflicting.

CPR is provided to every patient without his/her consent, unless differently stated. Actually, CPR accompanies every patient who is dying in the hospital and is routinely applied for legal purposes. However, cardiac resuscitation may restore cardiac function but does not prevent death; it merely prolongs the dying process. The appropriateness of CPR in cancer patients is an important clinical and ethical issue. Early and timely applied communication between patients, family and treating clinicians remains the best form of decision-making for CPR among patients with cancer. DNAR decision is an issue that requires early, clear and honest communication between clinicians and patients and relatives when relevant, in order to understand the proper timing for such a conversation, based on realistic facts and individuality.

The decision to apply or not CPR is complex and requires knowledge of patients' underlying diseases, functional status, such as KPS, and patient wishes and autonomy. Every patient is unique, and when it comes to end-of-life decisions flexibility and understanding from physicians as well as his or her wishes is necessary and should be respected.

It is also important to inform honestly patients and their relatives, when relevant, regarding CPR efficacy, survival to hospital discharge, subsequent quality of life, and overall survival after successful CPR and that successful resuscitation does not alter the underlying malignancy. However, more data are needed regarding the actual efficacy of CPR in an unselected patient population with cancer, such as the predictors of survival, quality of life of survivors, post-resuscitation morbidity, place of discharge (e.g. home, nursing home, hospice) and period of life gained after a successful CPR.

Another issue regarding cancer patients is ICU admission since admission of cancer patients to the ICU can no longer be considered futile [24]. Patients with good performance status, who are at the initial phase of their malignant disease and with life-extending treatment options available, should be regularly admitted to the ICU, while patients being only in palliative care should not. However, data available when ICU admission is considered are not sufficient to identify patients who are likely to benefit from ICU management [24].

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