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Clinical Paper

What is the outcome of cancer patients admitted to the ICU after cardiac arrest? Results from a multicenter study☆

B. Champigneulle[a,h,*], S. Merceron[b], V. Lemiale[c], G. Geri[a,h,i], D. Mokart[d], F. Bruneel[b], F. Vincent[e], P. Perez[f], J. Mayaux[g], A. Cariou[a,h,i], E. Azoulay[c,j]

[a] Medical Intensive Care Unit (ICU), Cochin University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France
[b] ICU, Mignot Hospital, Versailles, France
[c] Medical ICU, Saint Louis University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France
[d] Medical ICU, Paoli Calmette Institute, Marseille, France
[e] Medical ICU, Avicenne University Hospital, Assistance Publique – Hôpitaux de Paris, Bobigny, France
[f] Medical ICU, Nancy University Hospital, Nancy, France
[g] Medical ICU, La Pitié-Salpêtrière University Hospital, Assistance Publique – Hôpitaux de Paris, Paris, France
[h] Paris Descartes University, Sorbonne Paris Cité, Paris, France
[i] INSERM U970 Sudden Death expertise Center, Paris Cardiovascular Research Center, Paris, France
[j] Paris 7 University, Paris, France

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ABSTRACT

Aim: Low survival rate was previously described after cardiac arrest in cancer patients and may challenge the appropriateness of intensive care unit (ICU) admission after return of spontaneous circulation (ROSC). Objectives of this study were to report outcome and characteristics of cancer patients admitted to the ICU after cardiac arrest.
Methods: A retrospective chart review in seven medical ICUs in France, in 2002–2012. We studied consecutive patients with malignancies admitted after out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA).
Results: Of 133 included patients of whom 61% had solid tumors, 48 (36%) experienced OHCA and 85 (64%) IHCA. Cardiac arrest was related to the malignancy or its treatment in 47% of patients. Therapeutic hypothermia was used in 51 (41%) patients. The ICU mortality rate was 98/133 (74%). Main causes of ICU death were refractory shock or multiple organ failure ($n = 64$, 48%) and neurological injury ($n = 27$, 20%); 42 (32%) patients died in ICU after treatment-limitation decisions. Twenty-four (18%) patients were discharged alive from the hospital. Overall 6-month survival rate was 14% (18/133, 95% confidence interval, 8–21%). Survival rates at ICU discharge and after 6 months did not differ significantly across type of malignancy or between the OHCA and IHCA groups, and neither were they significantly different from those in matched controls who had cardiac arrest but no malignancy.
Conclusions: Even if low, the 6-month survival rate of 14% observed in cancer patients admitted to the ICU after cardiac arrest and ROSC may support the admission of these patients to the ICU and may warrant an initial full-code ICU management.

1. Introduction

Survival after cardiac arrest remains low despite major advances in management during resuscitation and after the return of spontaneous circulation (ROSC).[1–3] Overall hospital survival has been estimated at less than 10% after out-of-hospital cardiac arrest (OHCA) and about 15% after in-hospital cardiac arrest (IHCA).[4–7] Few data are available on survival rates in vulnerable populations such as elderly individuals or patients with malignancies.[8–10] Cancer patients were formerly considered as poor candidates to ICU admission. However, substantial improvements in the survival of patients with malignancies admitted to the ICU have been achieved in recent years.[11–13] These improvements may be ascribable to progress in cancer treatments, better intensive care strategies, and closer collaboration between oncologists and hematologists.[14]

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* Corresponding author at: Medical Intensive Care Unit, Cochin Hospital, Assistance Publique – Hôpitaux de Paris (AP-HP), 27 rue du Faubourg Saint-Jacques, 75014 Paris, France.
E-mail address: benoit.champigneulle@cch.aphp.fr (B. Champigneulle).

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Previous studies have assessed the management and outcomes of patients with malignancies admitted to the ICU after cardiac arrest.[10,15–19] Survival rates were usually low, particularly in the subgroups with metastatic solid tumors or hematological malignancies.[10,15–17] These low rates may challenge the appropriateness of cardiopulmonary resuscitation (CPR), the triage decision to ICU admission and other life-supporting interventions after ROSC in cancer patients. However, most of these studies were done years ago and therefore fail to reflect recent advances in the ICU management of cardiac arrest and patients with cancer.

The primary aim of this study was to evaluate outcomes of patients with malignancies admitted to the ICU after cardiac arrest followed by ROSC. Our secondary objectives were to describe the epidemiology and ICU management of these patients. To meet these objectives, we retrospectively reviewed the medical records of patients admitted to seven French ICUs.

2. Methods

2.1. Study design and patients

We retrospectively reviewed the medical records of patients admitted between 2002 and 2012 to seven medical ICUs involved in research on patients with malignancies (*Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique*, GRRROH) and having a policy of broad ICU admission for patients with malignancies. We identified consecutive patients aged 18 years or older who were admitted after OHCA or IHCA followed by ROSC and who had solid or hematological malignancies. In the seven involved hospitals, cardiac arrest patients were exclusively managed in medical ICU and patients with ROSC following IHCA on the wards were systematically directly referred to the ICU. Exclusion criteria were cardiac arrest in the ICU or during surgery and malignancy in remission for at least 5 years. According to French law on retrospective and observational studies, neither ethics committee approval nor informed consent was required for this study. Data used for the study were collected in an anonymized file.

2.2. Patient management

International guidelines[2] were followed, particularly regarding the target temperature during therapeutic hypothermia. Diagnostic and therapeutic procedures (*e.g.*, coronary angiogram, percutaneous coronary intervention, thrombolysis, brain or chest computed tomography) were performed at the discretion of the physicians in charge of each patient. Renal replacement therapy (RRT) was used either continuously or discontinuously depending on standard practice at each center. A thorough clinical neurological evaluation was performed, followed by an electroencephalogram and/or somatosensory evoked potential recording if deemed appropriate. Treatment-limitation decisions were considered in patients with a poor neurological prognosis or with refractory shock and multiple organ failures with or without recurrent cardiac arrest (post-cardiac arrest syndrome). Criteria for making treatment-limitation decisions were the same in all seven study ICUs and remained unchanged throughout the study period (Fig. S1 in the electronic supplement).

2.3. Data acquisition

The medical charts were reviewed for information on the underlying malignancy, characteristics of the cardiac arrest according to the Utstein style,[20] and treatments used in the ICU. The Knaus score was determined, as well as the Charlson comorbidity index with and without the points related to the malignancy.[21,22] Poor baseline general health was defined as a Knaus score C or D. Leukopenia was defined as a leukocyte count lower than 1000 mm^{-3}.[12] Baseline status of the malignancy was categorized as uncontrolled disease (newly diagnosed, recurrent, or progressive disease) or controlled disease (controlled or in remission for less than 5 years).[23,24] The possible contribution of the malignancy or its treatment to the cardiac arrest was assessed based on the cause of cardiac arrest, after reviewing case by three of the authors (BC, SM and VL). Vital status was determined by querying the patient's usual physician or public records office at ICU discharge and 6 months after ICU admission. The Cerebral Performance Categories (CPC) scale[25] was used to assess neurological outcomes at ICU discharge; scores of 1 or 2 were classified as good outcomes and scores of 3–5 as poor outcomes. Causes of death related to cardiac arrest in the ICU were defined as previously described.[26]

2.4. Comparison with cardiac arrest patients free of known malignancies

To further appreciate the survival rate of cardiac arrest patients with malignancies, a comparison was performed with a control group of OHCA patients without known malignancies issued from the French Parisian database, which was previously described.[26] A crude comparison of both ICU and 6-months survival rate was performed between unpaired patients with and without malignancies. This comparison was repeated by using matched controls randomly selected from the database with a 1/1 ratio. For each patient with malignancy (cases), a control was selected at random among individuals who met the matching criteria, namely, age, gender, whether cardiac arrest occurred in a public place, whether cardiac arrest was witnessed, whether CPR was delivered by a bystander, initial cardiac rhythm, time from collapse to ROSC, and cause of cardiac arrest (probably cardiac or other).

2.5. Statistical analysis

Continuous variables were described as median [25th–75th percentiles] and compared using the Mann–Whitney *U* test. Categorical variables were described as *n* (%) and compared using the chi-square test or Fisher's exact test as appropriate. Percentages were calculated using the number of patients without missing data as the denominator. Variables with more than 15% of missing data were identified. In subgroups of interest (solid *versus* hematological malignancies and OHCA *versus* IHCA), 6-month survival was estimated by plotting univariate Kaplan–Meier curves and compared using the log-rank test. *P* values lower than 0.05 were considered significant. All statistical analyses were performed using GraphPad Prism® v5.0 (GraphPad Software, San Diego, CA, USA) or STATA v11.0 (Lakeway Drive, TX, USA).

3. Results

3.1. Study patients

During the study period (2002–2012), 213 patients with malignancies were admitted to the seven participating ICUs after OHCA or IHCA followed by ROSC. Among them, 133 were included in the study (Fig. 1).

Table 1 reports the main patient characteristics. Sites of solid malignancies were the lung ($n = 27$, 20%), prostate ($n = 12$, 9%), urinary tract or kidney ($n = 8$, 6%), head and neck ($n = 8$, 6%), breast ($n = 7$, 5%), colon and rectum ($n = 6$, 5%), and other ($n = 13$, 10%). Spread of solid malignancies was local and regional in 50 (38%) patients, metastatic in 27 patients (20%), and unknown in 4 patients (3%). Hematological malignancies consisted of acute leukemia ($n = 13$, 10%), high-grade lymphoma ($n = 13$, 10%),

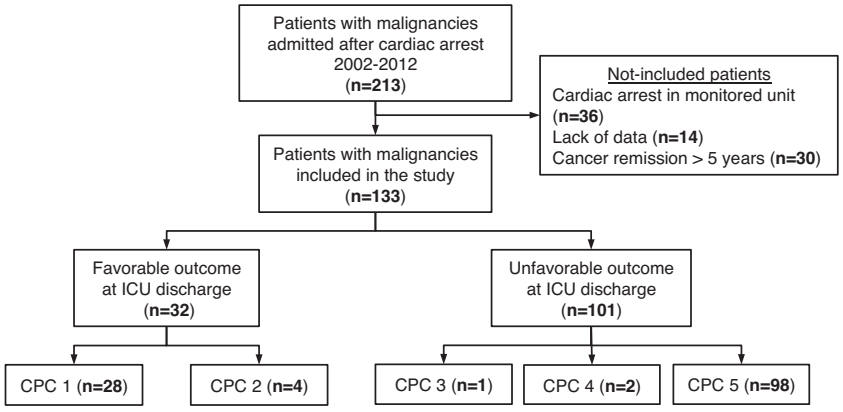

Fig. 1. Flowchart. ICU, intensive care unit; CPC, cerebral performance category.

low-grade lymphoma (n = 12, 9%), multiple myeloma (n = 7, 5%), and other (n = 7, 5%). Five (4%) patients with hematological malignancies had received allogeneic stem cell transplantation. No significant differences were apparent between the solid and hematological malignancy groups regarding age, sex ratio, previous chronic health status, Charlson comorbidity index without malignancy points, or disease status at admission (data not shown). The group with hematological malignancies had a higher proportion of patients with chemotherapy in the past month than did the group with solid malignancies (54% *vs.* 31%, P = 0.01).

3.2. Cardiac arrest characteristics (Table 2)

OHCA was more common in the solid malignancy group than in the hematological malignancy group (47% *vs.* 19%, respectively; P < 0.01). Compared to the IHCA group, the OHCA group had higher proportions of patients with a presumed cardiac cause of CA (33% *vs.* 15%, respectively; P = 0.03) and with an initial shockable rhythm (28% *vs.* 10%, respectively; P = 0.02). Our retrospective review supported a role for the malignancy or its treatment in the occurrence of cardiac arrest in 58/124 (47%) patients (Table S1). CPR administered by a bystander was more common in the IHCA group than in the OHCA group (85% *vs.* 38%, P < 0.01); the IHCA group had shorter times from collapse to first CPR attempt (0 [0–0] min *vs.* 5 [0–10] min, P < 0.01) and from collapse to ROSC (10 [5–20] min *vs.* 21 [14–35] min, P < 0.01).

Coronary angiogram was performed in 21 (16%) patients and was followed by a percutaneous intervention in 4 (3%) patients. Brain CT and chest CT were each performed in 31 (23%) patients.

3.3. ICU management

All patients received mechanical ventilation at ICU admission; duration of mechanical ventilation was 2 [1–6] days. Leukopenia was noted at ICU admission in 10 (10%) patients (data missing for 29 patients). Therapeutic hypothermia was used in 51 (41%) patients. Inotrope or vasoactive drugs were administered to 103 (82%) patients after ICU admission, for 2 [1–3] days. Renal replacement therapy (continuous or discontinuous) was used in 36 (28%) patients. Median ICU stay length was 2 [1–8] days. At least one ICU-acquired infection was diagnosed in 24 (19%) patients.

Table 1
Main characteristics of the 133 study patients.

Variable	
Age (years), median [IQR]	66 [57–76]
Males, *n* (%)	93 (70%)
Charlson comorbidity index, median [IQR]	
With malignancy points	7 [5–8]
Without malignancy points	3 [2–5]
Poor chronic health status (Knaus C or D), *n* (%)	70 (53%)
Underlying malignancy, *n* (%)	
Solid tumor	81 (61%)
Hematological malignancy	52 (39%)
Disease status at admission, *n* (%)	
Newly diagnosed	35 (28%)
Recurrent or progressive disease	43 (35%)
In remission <5 years or controlled	45 (37%)
Time since cancer diagnosis (months),[a] median [IQR]	12 [2–31]
Chemotherapy in past month, *n* (%)	49 (40%)

IQR, interquartile range.
[a] Data missing for more than 15% of patients.

Table 2
Cardiac arrest characteristics in the 133 patients.

Variable	
Location, *n* (%)	
In-hospital cardiac arrest	85 (64%)
Out-of-hospital cardiac arrest	48 (36%)
Bystander witness, *n* (%)	112 (93%)
Bystander CPR,[a] *n* (%)	73 (66%)
Initial shockable rhythm[a]	18 (17%)
Epinephrine dose (mg), median [IQR]	3 [1–6]
Intervals,[a] median [IQR]	
Collapse-to-first CPR attempt (min)	0 [0–5]
Collapse-to-ROSC (min)	15 [8–30]
Cause of cardiac arrest, *n* (%)	
Cardiac[b]	29 (22%)
Hypoxic[c]	54 (40%)
Pulmonary embolism	12 (9%)
Miscellaneous[d]	20 (15%)
Unknown	18 (14%)

IQR, interquartile range; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.
[a] Data missing for more than 15% of patients.
[b] Ventricular arrhythmia and/or coronary artery occlusion.
[c] Including cardiogenic pulmonary edema in the absence of acute myocardial infarction.
[d] Septic shock (n = 8, 6%), anaphylaxis (n = 3, 2%), and tumor lysis syndrome (n = 2, 2%).

Table 3
Differences between ICU survivors and nonsurvivors.

Variable	ICU survivors ($n = 35$)	ICU nonsurvivors ($n = 98$)	P value
Age (years), median [IQR]	68 [60–79]	65 [57–75]	0.16
Males, *n* (%)	25 (71%)	68 (69%)	0.49
Poor chronic health status (Knaus C or D), *n* (%)	12 (34%)	58 (59%)	0.02
Underlying malignancy, *n* (%)			
Solid tumor	20 (57%)	61 (62%)	0.69
Hematological malignancy	15 (43%)	37 (38%)	
Disease status at admission, *n* (%)			
Newly diagnosed	8 (24%)	27 (30%)	0.75
Recurrent or progressive disease	13 (38%)	30 (34%)	
In remission <5 years or controlled	13 (38%)	32 (36%)	
Location, *n* (%)			
In-hospital cardiac arrest	25 (71%)	60 (61%)	0.31
Out-of-hospital cardiac arrest	10 (29%)	38 (39%)	
Bystander, *n* (%)	33 (100%)	79 (91%)	0.10
Initial shockable rhythm,[a] *n* (%)	9 (30%)	9 (12%)	0.04
Epinephrine dose (mg), median [IQR]	1 [0–4]	3 [2–7]	<0.01
Intervals,[a] median [IQR]			
Collapse-to-first CPR attempt (min)	0 [0–1]	0 [0–6]	0.02
Collapse-to-ROSC (min)	6 [3–10]	20 [10–30]	<0.01
Presumed cardiac cause of cardiac arrest, *n* (%)	14 (40%)	15 (15%)	<0.01
Length of ICU stay (days), median [IQR]	5 [2–11]	1 [0–5]	<0.01

IQR, interquartile range; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.
[a] Data missing for more than 15% of patients.

3.4. Outcomes at ICU discharge and hospital discharge

Of the 133 patients, 98 (74%) died in the ICU (Fig. 1), including 61 (46%) who died within 2 days after admission. Cause of death was refractory shock with multiple organ failure (including recurrent cardiac arrest after ICU admission) in 64 (48%) patients and neurological injury in 27 (20%) patients, including 4 (3%) with brain death. Seven patients died after treatment-limitation decisions based on advanced underlying cancer or poor health status. Treatment-limitation decisions (including a decision not to readmit to the ICU) were taken for 49 (37%) patients, 3 [1–10] days after ICU admission; of these patients, 42 (86%) died in the ICU, 5 others died in the hospital and 2 patients were discharged alive. Table 3 reports the differences between ICU survivors and nonsurvivors. Of the 35 (26%) patients alive at ICU discharge (Fig. 1), 32 (91%) had good neurological outcomes. Hospital length of stay after ICU discharge was 16 [7–33] days. However, 11 patients died in the hospital after ICU discharge, leaving 24 (18%) patients alive at hospital discharge, including 23 with good neurological outcomes and 1 with severe disability (CPC score 3).

3.5. Six-month survival

Overall 6-month survival rate was 14% (18/133, 95% CI, 8–21%). Kaplan–Meier estimates showed no significant difference in 6-month survival between patients with solid *vs.* hematological malignancies (Fig. 2A) or between patients with IHCA *vs.* OHCA (Fig. 2B). Characteristics of these surviving patients are described in Table S2.

3.6. Comparison with cardiac arrest patients free of known malignancies

Table S3 reports the unpaired data analysis, which reveals a higher 6-month mortality rate in patients with malignancies by comparison with unselected controls. Among these unselected controls, we identified a matched control for 88 patients with malignancies. Neither ICU mortality nor 6-month mortality differed significantly between the cases and controls (Table S4). The estimated 6-month survival rate was significantly different in the unmatched comparison of cardiac arrest patients with and without malignancies but not in the matched comparison (Fig. S2).

4. Discussion

In our retrospective study of 133 patients with malignancies who recovered spontaneous circulation after cardiac arrest, 23 (17%) patients were alive at hospital discharge with a favorable neurologic outcome (CPC score 1 or 2) and 18 (14%) were alive after 6 months. The 6-month survival rate in our patients with malignancies was not significantly different from that in a matched control group of patients with OHCA and no malignancies. Cardiac arrest is not a common reason for ICU admission of patients with malignancies. In a recent epidemiologic study in 17 ICUs of the GRRROH network, only 3% of ICU admissions in a large population of patients with hematological malignancies were due to cardiac arrest.[27] Hospital mortality in this subgroup was 76.7% and admission after cardiac arrest was an independent risk factor for mortality. Even if most patients with malignancies and cardiac arrest are probably not eligible to CPR and ICU admission after ROSC, ours results are important as resuscitation of cardiac arrest is probably useful in some of them. Thus, our study adds updated data about prognosis and post-cardiac arrest cares in ICU in the specific subgroup of cancer patients. We believe that our data may support ICU admission of selected cancer patients with ROSC after cardiac arrest. This admission may be associated with an initial full-code ICU management, reassessed after 2 or 3 days, depending to the clinical course (especially neurological recovery or not), as proposed for cancer patients admitted in ICU in other circumstances.[14]

The few available studies of cardiac arrest in patients with malignancies included heterogeneous populations of patients.[10,15–19] Furthermore, most of these studies were done years ago,[15–19] and in the interval substantial progress has been made in the management of cardiac arrest patients.[1–3] In a metaanalysis including

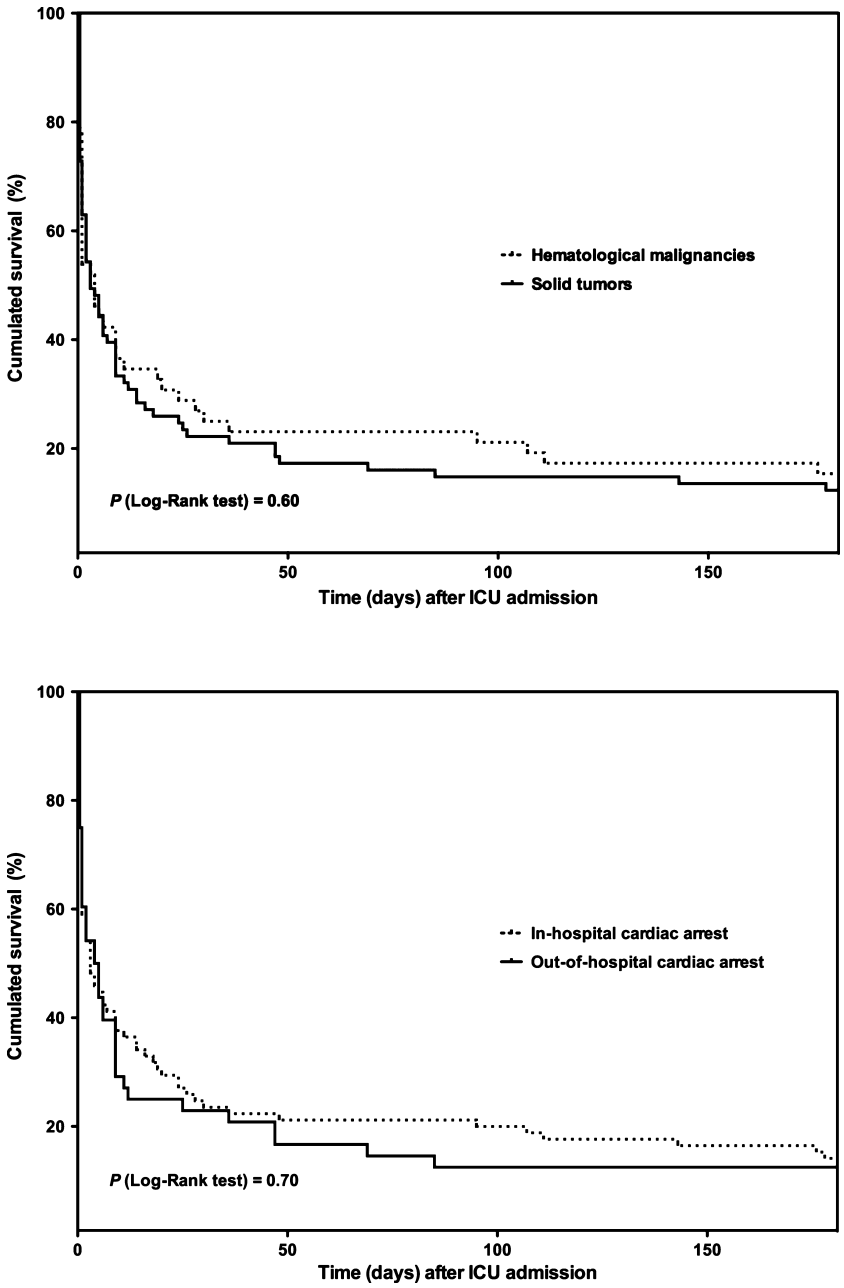

Fig. 2. Kaplan–Meier estimates of 6-month (181-day) survival in patients with malignancies admitted to the ICU after cardiac arrest followed by return of spontaneous circulation, according to (A) underlying malignancy (solid *vs.* hematological malignancies) and (B) location of cardiac arrest (in-hospital *vs.* out-of-hospital cardiac arrest). ICU, intensive care unit.

more than 1700 IHCA patients with malignancies, overall hospital survival was lower than in our study (6.2%; 95% CI, 3.2–9.1%).[10] The results of this metaanalysis should be interpreted with caution because the population in the included studies was probably very heterogeneous (*e.g.*, solid and hematological malignancies, cardiac arrest in the ICU and wards) and several studies are weakened by small sample sizes. Comparison with our results is difficult as we included only patients with ROSC after cardiac arrest (without take into account neither patients who were not resuscitated nor those in whom resuscitation failed to restore spontaneous circulation). Same, we did not study patients who experienced cardiac arrest while in monitoring units. However, these patients differ in many ways from those who go into cardiac arrest while on wards. Cardiac arrest in the postanesthesia care unit or operating room may carry a relatively good prognosis, since qualified personal and appropriate equipment and drugs are immediately available.[28] Conversely, in the ICU, cardiac arrest often occurs in patients with shock and mechanical ventilation and may therefore carry a poorer prognosis, particularly in patients with malignancies.[10,29]

In our study, either the cancer or cancer treatments were felt to contribute to the occurrence of cardiac arrest in as many as 47% of patients. Few studies have investigated the causes of cardiac arrest in patients with malignancies. Of 49 patients admitted to a cancer center ICU after cardiac arrest, 8 had drug toxicities and 2 tumor lysis syndrome.[16] Further studies should investigate the specific causes of cardiac arrest in patients with malignancies. Patients with malignancies who are admitted to the ICU should be screened for factors likely to contribute to cardiac arrest.

We observed a relative low rate (41%) of targeted temperature management in our study. This low rate may be explained by the

high part of both IHCA and initial non-shockable rhythm in our population (respectively 64% and 83%). However, due to the retrospective design of the study, we cannot rule out that this low rate also reflected a poor expected prognosis by the in charge physician and then corresponded with a treatment limitation. Likewise, it was not possible to ascertain that cancer patients received similar in-ICU treatments as compared to controls.

ICU survivors and nonsurvivors in our study had no significant differences regarding the type or status of the malignancies. This finding is at variance with previous studies done on cardiac arrest in patients with malignancies[10,17] but is consistent with several ICU studies.[12,13,30] Conceivably, patients with active or extended malignancies may receive greater intensity of life-supporting treatments, which may eliminate any difference in survival. Nonsurvivors had a worse baseline health status, in keeping with early studies.[18,23,24,30] The factors that influenced survival in our study were the same as in previous studies of unselected patients.[2,4]

Our study has several limitations. First, the retrospective design may have induced selection bias and a substantial rate of missing data. Accurate data on resuscitation duration may be unavailable due to lack of a witness, inability of bystanders to record times of events, multiplicity of actors, and clock inaccuracies.[20] Second, we did not study patients who died on scene (*i.e.* patients on whom CPR was not attempted because of presumed futility or previously set do-not-resuscitate order as patients with unsuccessful attempt). Therefore, our study population was highly selected and the observed survival rate must be interpreted cautiously. Third, we had no information on quality of life or subsequent treatments in the survivors. These two points deserve to be addressed in further studies. Finally, our population was heterogeneous regarding malignancy type and status and location of cardiac arrest. These characteristics may influence the chances of survival. However, ICU admission after cardiac arrest and ROSC is a rare event[27] and, consequently, the use of restrictive inclusion criteria would have resulted in a smaller sample size despite the multicenter design and 11-year inclusion period.

In conclusion, our data indicate a global 6-month survival rate of 14% after ROSC in cardiac arrest patients with malignancies and a similar survival rate when patients were matched with a control group. Accordingly, our data should help ICU physicians for triage decision to ICU admission of these patients after ROSC and may warrant an initial full-code ICU management. Nevertheless, the subsequent treatment strategy should be assessed after a few days in the light of the response to intensive care and status of the underlying malignancy.

Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Author contributions

BC, SM, VL, and GG contributed to conceive and design the study; collect, analyze, and interpret the data; and write the manuscript.

AC and EA contributed to conceive and design the study and to write the manuscript.

DM, FB, FV, PP, and JM contributed to collect the data.

All authors read and approved the final version of the manuscript.

This original manuscript has not been published in all or in part and is not under consideration for publication by another journal.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2015.04.011

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