

## ORIGINAL REPORT

## FEASIBILITY AND SAFETY OF ACTIVE PHYSIOTHERAPY IN THE INTENSIVE CARE UNIT FOR INTUBATED PATIENTS WITH MALIGNANCY

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**Objectives:** Physiotherapy leads to improvements in critically ill patients who receive mechanical ventilation. However, cancer patients have not been included in previous studies on this subject. This study explored the feasibility and safety of physiotherapy in the intensive care unit for patients with malignancy.

**Design:** Observational prospective single-centre study, comparing cancer and control patients.

**Patients:** All consecutive patients admitted to the intensive care unit who needed invasive mechanical ventilation for more than 2 days with no contraindication to physiotherapy were included in the study.

**Methods:** The main outcome was the proportion of physiotherapy sessions at the prescribed level in each group.

**Results:** A total of 60 patients were included within 1 year. A total of 576 days were screened for physiotherapy sessions and 367 physiotherapy-days were analysed (137 days for control patients and 230 days for cancer patients). The ratio of physiotherapy sessions performed/prescribed did not differ between groups: 0.78 (0.47–1) in the control group vs 0.69 (0.6–1) in the cancer group (odds ratio 1.18 (IC95% 0.74–1.89);  $p=0.23$ ). A sensitivity analysis including patient effect as random variable confirmed those results (odds ratio 1.16 (0.56–2.38),  $p=0.69$ ). Adverse events occurred with the same frequency in cancer patients and non-cancer patients.

**Conclusion:** Physiotherapy in cancer patients who require intubation is feasible and safe. However, only two-thirds of prescribed physiotherapy sessions were performed. Studies are warranted to explore the barriers to physiotherapy in the intensive care unit setting.

**Key words:** intensive care unit outcome; physiotherapy; cancer.

Accepted May 31, 2022; Epub ahead of print Aug 26, 2022

J Rehabil Med 2023; 55: jrm00299

DOI: 10.2340/jrm.v54.736

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## LAY ABSTRACT

Mobilization for intubated patients improves outcomes. However, patients with malignancy have not been included in previous studies exploring mobilization in the intensive care unit (ICU). This study explored the feasibility and safety of mobilization for intubated patients with malignancy. Intubated patients with and without cancer were included in an observational study. Each day, a mobilizing team, including a physiotherapist, decide on the mobilization level for individual patients, according to their awakening and motor status. The physiotherapist performed the physiotherapy sessions. The level obtained during physiotherapy sessions was compared with the prescribed level. A physiotherapy session was considered successful when the prescribed level was obtained. Statistical analysis of 27 non-cancer patients and 33 cancer patients did not reveal any differences in terms of the feasibility and safety of physiotherapy sessions. However, in this study, only two-thirds of prescribed physiotherapy sessions were performed. Barriers to the use of physiotherapy in the ICU for patients with malignancy should be explored.

Myopathy during intensive care unit (ICU) stay is frequent and leads to higher risk of mortality (1). In particular, when invasive mechanical ventilation and sedation are required, the patient may develop severe motor deficiency within several weeks. In that setting patients may severely disenable and start to improve after several weeks (2, 3). Several factors, such sepsis, inflammation and multi-organ failure may increase muscle damage (4). Such intensive care-acquired weakness has been associated with a longer duration of mechanical ventilation and higher risk of hospital-acquired infection (2, 5). There is no treatment for such reversible acquired weakness.

Early mobilization has been shown to decrease the duration of motor weakness (6, 7). Also, early mobilization is associated with a shorter length of stay in intensive care and in hospital (8). Although the dose and duration of physiotherapy sessions are not well codified, the Functional Independence Measure (FIM) score were shown to be increased at ICU discharge in patients who received early mobilization sessions (9, 10).

While rehabilitation in the ICU seems feasible for the majority of patients, patients with cancer have always been excluded from previous studies. However, in cancer patients receiving chemotherapy, exercise intolerance and asthenia can be frequent (11). Several factors may increase exercise difficulties: anaemia, digestive intolerance, and asthenia related to malignant disease. Moreover, in studies of critically ill patients, tolerance of exertion remains one of the major reasons for stopping physiotherapy sessions. Therefore, in patients with cancer, early mobilization may be compromised and the functional goals achieved could be lower than in other patients without cancer.

Patients with cancer are now numerous in the ICU. In the early 2000s, the mortality rate of such patients after ICU admission was very high. Admission to ICU, at that time, was questionable because most patients died in the ICU or could not receive any cancer treatment after discharge from ICU regarding their poor health. With outcome improvement in cancer treatment and ICU management, most of these patients survive an ICU stay (12). Such patients may need chemotherapy or other cancer treatment after discharge from the ICU (13). In that setting, the ability to receive treatment may also depend on performance status and muscular weakness. Early mobilization of such patients thus appears to be of importance and should be highlighted. The current study could promote early mobilization in cancer patients if the hypothesis of feasibility is confirmed.

The aim of this study was to assess the feasibility of physiotherapy in cancer patients in intensive care after intubation and mechanical ventilation.

## MATERIAL AND METHODS

This was an observational prospective, single-centre study in Saint Louis hospital, Paris. All intubated patients successively admitted to the ICU were screened for inclusion in the study. The hospital has 650 beds with more than 300 beds for patients with malignancy. More than 700 patients are admitted to the 12-bed ICU per year. Fifty percent of patients receive chemotherapy before or during their ICU stay. One physiotherapist works in this ICU during weekdays (5 days a week).

The study was approved by comite de protection des personnes (ethic committee) West 5 Rennes (number 18/037-3) and comité d'éthique de la (SRLF French intensive care society 17–50). Each patient or relative received information concerning the study and the data recorded. Informed consent was not required according to French law.

All patients over 18 years of age who were admitted to the ICU between 1 May 2018 and 14 July 2019, who received invasive mechanical ventilation for more than 48 h were included. Exclusion criteria were

moribund patients (simplified severity index IGS (indice de gravité simplifié) >85) or patients with an end-of-life decision. Other exclusion criteria were permanent contra-indication to physiotherapy (mostly neurological reasons), pregnancy, breastfeeding, patient not covered by medical insurance, or patient refusal.

Briefly, in this ICU, the physiotherapy session level was defined by a doctor and physiotherapist according to the Medical Research Council (MRC) score (14) and Richmond Agitation Sedation Scale (RASS) (15). The MRC score is associated with muscle weakness (from 0 (no muscle contraction) to 5 (normal strength) points in 12 muscular groups for a total of 60 points). RASS score assessed the consciousness (from -5 unrousable, to 0 alert and calm, and +5 combative). Each day, a medical student assessed the RASS and MRC scores for each patient intubated for more than 48 h. The prescribed level of physiotherapy each day was based on level of consciousness (RASS score) and muscle strength (MRC score) (Table SI). Then, the physiotherapist assessed the level of mobilization obtained during the session. The obtained level was compared with the prescribed level. When mobilization performed reached the prescribed level of physiotherapy, the physiotherapy session was defined as successful. A team including physiotherapist and ICU nurses performed all physiotherapy sessions during working hours, 5 days a week. Contra-indications and reasons not to perform physiotherapy sessions were recorded, when this happened. If patients did not get physiotherapy sessions because of an end-of life decision or non-attendance of the physiotherapist, the physiotherapy-day was excluded from the analysis. The number and type of complications related to early mobilization (tearing off material, haemodynamic or respiratory adverse event, or other) were recorded. Moreover, variables concerning organ failure and diagnosis were recorded for the entire the ICU stay.

The FIM (16) and MRC scores (14) at ICU discharge, length of stay in intensive care or in hospital, and mortality were also recorded for each patient. The FIM is a score to assess and grade the functional status of a person, based on the level of assistance he or she requires (17).

Shock status was defined as the need for a vasopressor.

### Data analysis

All consecutive patients hospitalized in the ICU were included over a period of 14 months while the same physiotherapist was present. Two groups of patients were compared (cancer patients and non-cancer patients).

The main objective was to assess the feasibility of physiotherapy in cancer patients. The primary endpoint was the proportion of physiotherapy sessions performed in cancer patients and non-cancer patients. The secondary objectives assessed the safety of physiotherapy sessions in cancer patients, and the occurrence of adverse events. Secondary endpoints were the proportion of physiotherapy sessions interrupted for intolerance, and the proportion of adverse events in each group.

The results were expressed as medians and 25th and 75th quartiles [Q1–Q3] for quantitative data, and numbers and percentages for categorical data. Quantitative variables were compared using Student’s *t*-test or Wilcoxon test in case of non-normal distribution. Qualitative variables were compared using  $\chi^2$  test or Fisher’s exact test, as appropriate. No imputation was performed on missing data. Univariate analysis comparing the characteristics and outcomes across the 2 groups of patients (patients with solid tumour or haematological malignancy and control patients) was performed.

The primary endpoint, the proportion of prescribed physiotherapy sessions performed, was compared in the cancer group and the non-cancer group. The primary endpoint was analysed with a mixed logistic regression model, including patient effect as random variable, and by the ratio of sessions performed at the prescribed level (analysed using weighted mixed logistic regression)

Secondary endpoints were analysed in the subgroup of patient-days for which physiotherapy was actually performed. At the patient level a weighted logistic model was used, and at the physiotherapy-day level a mixed logistic model (with a random patient effect) was used.

**RESULTS**

Within 14 months, 60 patients were included in the study. Fig. 1 summarizes the screened patients and reasons for exclusion. Non-included patients stayed (median, IQR) 10 (7–16.5) days in ICU and the mortality rate of non-included patients was 36% (15 patients).

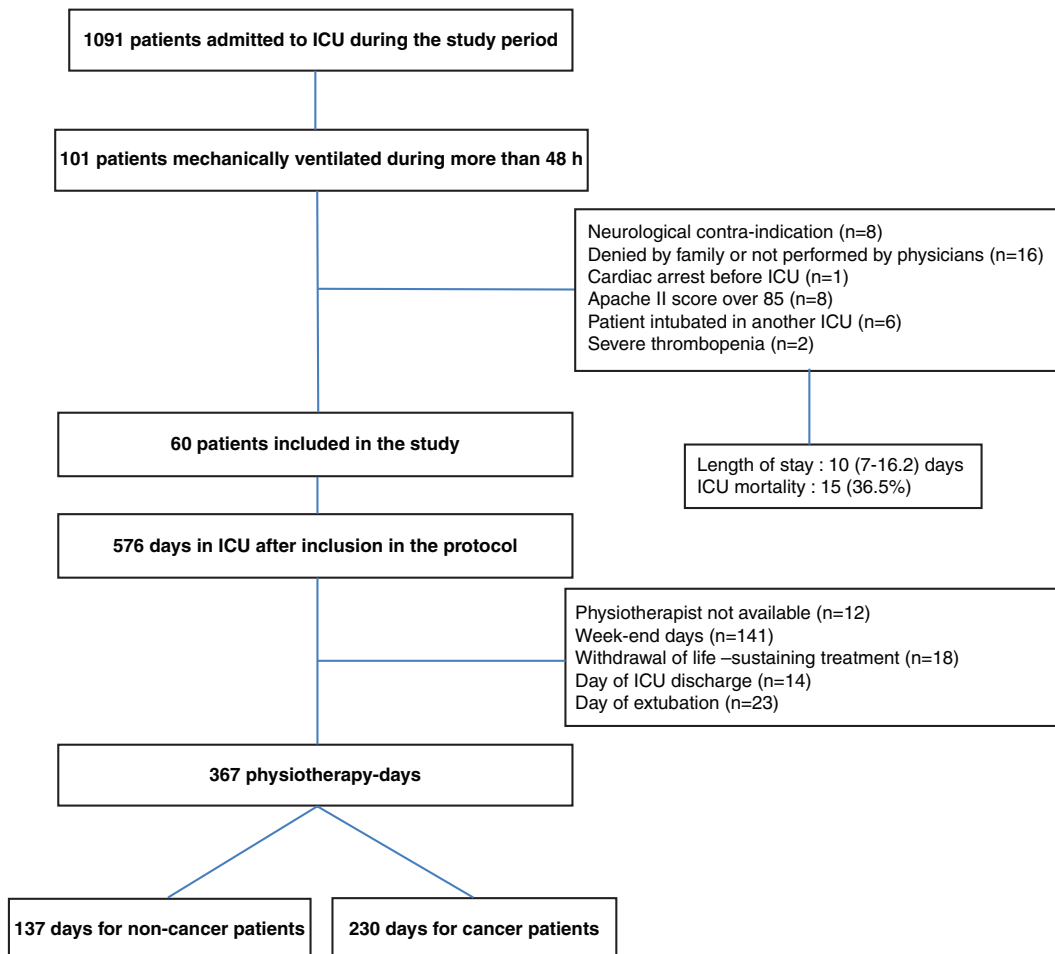


Fig. 1. Study flow chart.

Among the 60 studied patients, 36 (60%) were male, median age was 59.6 (46–67.8) years, with good performance status for 13 (21%) patients. The reasons for ICU admission were haemodynamic failure ( $n=20$ ; 33%), respiratory failure ( $n=29$ ; 48%), coma ( $n=3$ ; 5%) and multiple organ failure ( $n=8$ ; 13%). Twenty (33%) patients had neutropaenia at ICU admission, whereas 19 (32%) patients had anaemia and 29 (48%) patients had thrombopenia. Patients were admitted to ICU (median, IQR) 1.5 (0–10.7) days after hospital admission and were intubated within the 3 (2–5) first days. Twenty-eight patients (47%) received chemotherapy within the month before ICU admission or during their stay in ICU. Physiotherapy sessions started within (median, IQR) 3 (2–5) days after intubation. Patients stayed (median, IQR) 12.5 (9–20.25) days in ICU after inclusion in the study.

Among included patients, 33 had solid tumour or haematological malignancy and 27 were control patients. The characteristics of the groups at ICU admission are summarized in Table I. Briefly, control patients had more comorbidities at ICU admission, and were discharged earlier from ICU. Most cancer patients had neutropaenia (61%) and they started physiotherapy sessions later than control patients during the ICU stay.

The duration of acute respiratory distress syndrome (ARDS) and/or shock was longer in cancer patients.

During ICU stay, 576 physiotherapy-days were screened for physiotherapy sessions. On these days, the reasons physiotherapy was not performed were: weekend days ( $n=141$ ), physiotherapist was not available ( $n=12$ ), withdrawal of life-sustaining treatment was decided ( $n=18$ ), physiotherapy was not performed on the day of discharge from ICU ( $n=14$ ), or on the day of extubation ( $n=23$ ). All of these physiotherapy-days were excluded from the analysis. Thus, only 367 physiotherapy-days were analysed (137 days for control patients and 230 days for cancer patients) for the 60 patients. Fig. 1 summarizes why physiotherapy-days were not included in the analysis. There was no missing data on the primary endpoint. Each patient received (median, IQR) 4 (2–5) physiotherapy sessions. Of these, 3 (1–5) physiotherapy sessions were performed at the prescribed level. Fig. 2 summarizes the physiotherapy treatment for each patient. Most physiotherapy sessions at the prescribed level were delivered in the early days after intubation and at the end of the ICU stay.

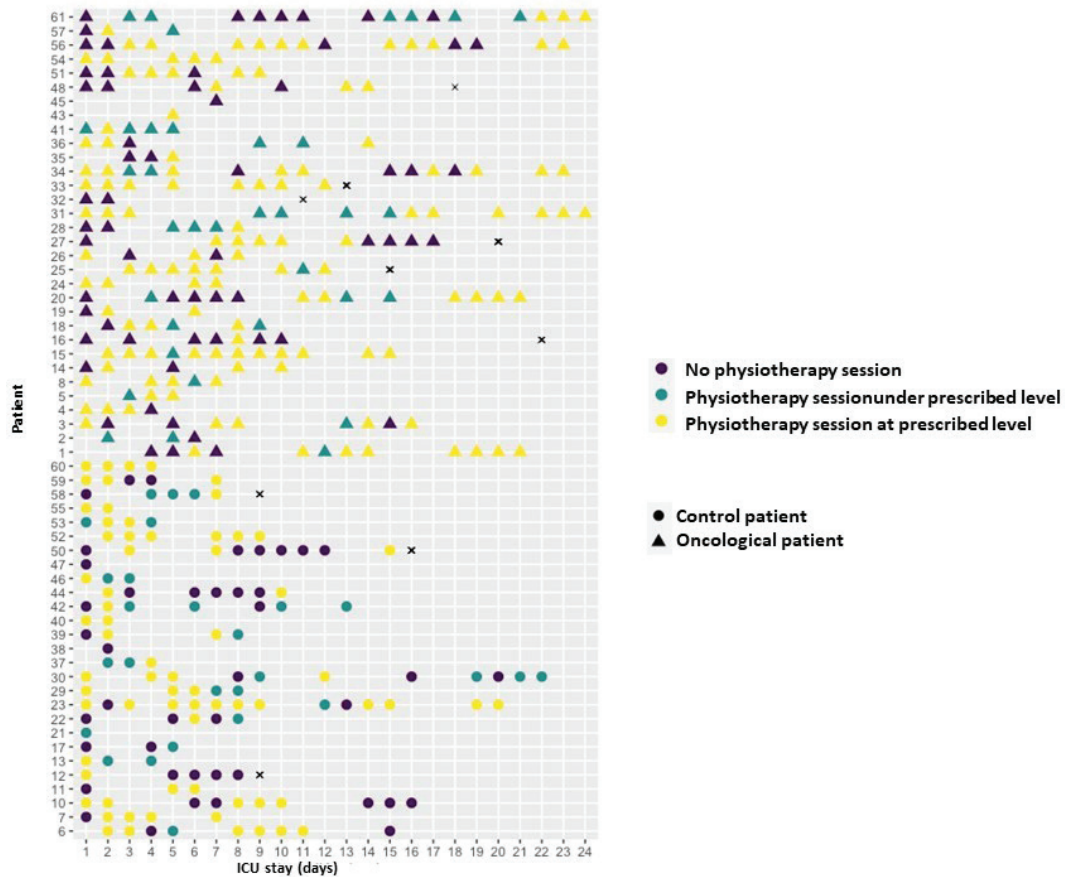
The ratio between physiotherapy performed over physiotherapy prescribed did not differ between groups: (mean and interquartile range) 0.78 (0.47–1)

**Table I.** Characteristics at intensive care unit (ICU) admission and outcomes according to cancer status

Variables	Patient with cancer ( $n=33$ )	Patients without cancer ( $n=27$ )	$p$ -value
Age (years) m, (IQR)	57 (44–69.5)	62 (47–67)	0.41
Sex, male, $n$ (%)	21 (64)	15 (56)	0.71
Comorbidities, $n$ (%)			
Cardiovascular	9 (27)	14 (52)	0.09
Pulmonary	9 (27)	12 (44)	0.26
Kidney	1 (3)	6 (22)	0.04
Diabetes	2 (6)	11 (41)	0.002
Neurological disease	1 (3)	0(0)	
Performance status > 2 $n$ (%)	6 (22)	7 (21)	
Reason for ICU admission $n$ (%)			0.30
Haemodynamic failure	14 (42)	6 (22)	
Acute respiratory failure	13 (39)	16 (59)	
Coma	1 (3)	2 (7)	
Multi-organ failure	5 (15)	3 (11)	
SOFA score at ICU admission	8 (6.5–10)	11 (8–14)	0.05
Apache II score at ICU admission	61 (48–72)	42 (32–53)	0.003
Neutropaenia at admission	20 (61)	0 (0)	<0.001
Thrombopaenia	24 (73)	5 (19)	<0.001
Length of time between ICU admission and mobilization days (median and IQR)	9 (5–21)	5 (3–8.5)	0.008
Length of time between intubation and mobilization days (median and IQR)	4 (3–6)	3 (2–4)	0.008
ARDS, $n$ (%)	14 (42)	8 (30)	0.10
ARDS, criteria duration days (median and IQR)	2 (1.25–4)	2 (2–3)	0.78
Length of ICU stay days (median and IQR)	16 (10–23)	10 (7–15.5)	0.004
RASS score at day 1 (from –5 to +5) (median and IQR)	–3 (–4.2 to –1.8)	–3 (–4–0)	0.40
MRC at day 1 (0–60) (median and IQR)	0 (0–2)	0 (0–30)	0.51
MRC at ICU discharge (48 patients) (median and IQR)	43 (36–48)	46 (40–49)	0.79
FIM at ICU discharge (39 patients) (0–126) (median and IQR)	55 (41–70)	45 (32–68)	0.34
End-of-life decision, $n$ (%)	3 (1)	2 (0.7)	0.81
ICU mortality, $n$ (%)	7 (21)	3 (11)	0.49
Length of ICU stay days (median and IQR)	16 (10–23)	10 (7–15.5)	0.004

SOFA: sequential organ failure score; ARDS: acute respiratory distress syndrome; RASS: Richmond Agitation Sedation Scale; MRC: Medical Research Council score; FIM: Functional Independence Measure; ICU: intensive care unit; IQR: interquartile range.





**Fig. 2.** Physiotherapy session for each patient. In this lolly-plot each line represents a patient followed for 24 days. For each patient, each prescribed physiotherapy session is represented (not performed, performed at lower level, performed at prescribed level). Days without any physiotherapy were not analysed (contra-indication or patients discharged from the intensive care unit (ICU)). In the upper part of the diagram, cancer patients are represented, and in the lower part of the diagram, control patients are represented.

in the control group vs 0.69 (0.6–1) in the cancer group (OR 1.18 (0.74–1.89;  $p=0.23$ ). Table II summarizes the physiotherapy sessions in cancer and non-cancer patients. A sensitivity analysis was performed using a mixed model with patients as random variable. The results did not differ between patient groups: 96 (70%) physiotherapy sessions performed in the control group and 168 (73%) sessions in the cancer group (OR 1.16 (0.56–2.38);  $p=0.69$ ).

The reasons why physiotherapy sessions were not performed are summarized in Table III. The main reasons were neurological contra-indication in 1 patient with brain abscess and brain hypertension during several days. Other reasons occurred in patients who got worse between physical examination and physiotherapy session (acute respiratory failure or haemodynamic failure).

Physiotherapy was performed at the prescribed level for (mean and interquartile range) 0.36 (0.2–0.67) prescribed physiotherapy sessions in the control group vs (mean and interquartile range) 0.6 (0.33–0.69) in cancer group (OR 1.29 (0.85–1.97),  $p=0.27$ ).

Severe adverse events occurred during 10 sessions (Table II). The number of adverse events did not differ between the cancer and control groups ( $n=7$  (3%) vs  $n=3$  (2.2%),  $p=0.87$ ). Severe adverse events were hypoxemia leading to cancellation of the session ( $n=5$ , 2.1%), shock during physiotherapy session related to hospital-acquired pneumonia for 1 patient and acute respiratory failure related to exacerbation of chronic obstructive pulmonary disease (COPD) for 1 patient ( $n=2$ , 0.8%), severe arterial hypertension ( $n=2$ , 0.9%), and tachycardia ( $n=1$ , 0.4%). Beside these severe adverse events, physiotherapy was stopped in cases of tiredness for 9 (3.9%) sessions in the cancer group and 10 (7.2%) sessions in the control group ( $p=0.24$ ).

At discharge from ICU 7 (21%) patients in the cancer group and 3 (11%) patients in the control group died.

Among the surviving patients, the last MRC score recorded before discharge from ICU was 43 (36–48) in the cancer group vs 46 (40–49) in the control group ( $p=0.79$ ). FIM score was assessed for 39 (65%) patients at ICU discharge and was 55 (41–70) in the

**Table II.** Physiotherapy ratio according to the group

Variables	Patient with cancer (n = 33)	Patients without cancer (n = 27)	OR	p-value
Physiotherapy performed (n/prescribed) (%)	168/230 (73)	96/137 (70)	1.16 (0.56–2.38)	0.69
Ratio (physiotherapy performed/ prescribed)	0.69 (0.6–1)	0.78 (0.47–1)	1.18 (0.74–1.89)	0.23
Ratio performed/prescribed with correct level	0.6 (0.33–0.69)	0.36 (0.2–0.67)	1.29 (0.85–1.97)	0.27
Severe adverse events related to physiotherapy n (%)	7 (3)	3 (2.2)		0.87
Hypoxaemia leading to cancellation of session n	4	1		
Shock n	1	1		
Severe arterial hypertension n	1	1		
Tachycardia n	1	0		

OR: odds ratio.

**Table III.** Reasons for not performing physiotherapy session

	Cancer patient n, %	Control patients n, %	p-value
Physiotherapy sessions n	230	137	
Agitation n (%)	3 (1.3)	1 (0.7)	0.12
Haemodynamic failure n (%)	8 (3.5)	8 (5.8)	0.09
Neurological contra-indication n (%)	23 (10)	15 (10.9)	0.12
Respiratory failure n (%)	13 (5.7)	6 (4.4)	0.12
Dialysis when physiotherapist was available n (%)	3 (1.3)	2 (1.5)	0.12
Pain n (%)	1 (0.4)	1 (0.7)	0.10
Leg haematoma n (%)	0 (0)	1 (0.7)	0.18
Declined by patient n (%)	2 (0.9)	0 (0)	0.18
Thrombosis n (%)	1 (0.4)	0 (0)	0.18
Not specified n (%)	8 (3.5)	7 (5.1)	
Total n (%)	62 (26.9)	41 (29.9)	0.54

cancer group and 45 (32–68) in the control group ( $p=0.34$ ).

### DISCUSSION

This prospective observational study shows that physiotherapy is feasible without adverse events in patients with malignancy who are admitted to ICU. Such patients were usually excluded from previous study (7, 10). However in our intensive care unit, patients with aplasia or receiving chemotherapy before or during ICU stay, usually received physiotherapy. This is the first study to compare non-cancer and cancer patients undergoing physiotherapy in the ICU.

In the current study, cancer patients stayed longer in the ICU than other patients. Yet, they received the same proportion of prescribed physiotherapy sessions as control patients. Most of those sessions occurred in the first and last days of the ICU stay. For patients who stay longer in the ICU, the impact of loss of muscular strength is highly important (18). In the last days of an ICU stay, rehabilitation is of importance in order to discharge patients who have still a high level of dependency. In contrast, patients who stay a shorter time in ICU may have less severe muscular weakness. Rehabilitation may then focus on more severe patients. The second point highlighted in this real-word study is the low number of physiotherapy sessions performed

during ICU stays. Physiotherapy sessions were performed on only two-thirds of days in the ICU.

Several barriers occurred that limited physiotherapy sessions. The first barrier was the team adhesion to physiotherapy. Several studies explored those barriers (9, 19). One recent study assessed those barriers with 10 scenarios analysed by a physician, nurse or physiotherapist (19). Haemodynamic or respiratory instabilities were the most frequent barriers, and lack of nurses to assist, and deep sedation were also frequent barriers. In the guidelines concerning physiotherapy, patients should receive physiotherapy sessions as soon as they stay more than 48h in ICU. However, due to severity of patients or sedation, patients may start physiotherapy course after few days in intensive care (20). However, most studies demonstrated safety and feasibility of early mobilization (21). In the current study, mobilization started within the (median, IQR) 3 (2–5) first days of mechanical ventilation, with a longer delay for cancer patients. Although, this delay may reflect patient’s severity and longer sedation time, those characteristics did not differ between the 2 groups. This delay may also reflect the team barrier for physiotherapy. However, when physiotherapy sessions were performed, the prescribed level of physiotherapy could be obtained. This was in accordance with a previous study (21). Indeed, the prescribed levels depend on patient examination. Some of the prescribed levels might be lowered according to clinical examination to avoid failure or adverse events. For example, when a patient is receiving renal replacement therapy, the prescribed physiotherapy level might be lower and the level obtained would be in accordance with the prescribed level. However, this level would not reflect muscle strength or patient effort (22). Another barrier came from the ICU team and was related to the lack of physiotherapists in the ICU. In our ICU, only 1 part-time physiotherapist performed all physiotherapy sessions, with assistance from a nurse.

The second important barrier may be related to the patient’s wishes. Some patients, when awake, declined physiotherapy sessions, mostly due to fear. Söderberg et al. recently performed a qualitative study

on patients who received physiotherapy during a stay in ICU (23). They found several kinds of experience from patient interviews, associated with negative and positive emotional features. The most positives ones were related to effort and cooperation with the team, but the most negative ones were related to fear and pain. Unfortunately, in the current study, patient experience was not assessed, but some patients declined physiotherapy sessions.

Physiotherapy remains of importance, particularly for cancer patients. Most of those patients need chemotherapy treatment after discharge from ICU and should be able to receive it. In a retrospective study, the lack of cancer treatment after discharge from ICU was associated with higher mortality (13). Indeed, only fit patients can receive chemotherapy. Thus, providing physiotherapy to increase muscular strength (24) and performance status in such patients remains of importance. The aim of admission to ICU should also include further treatment for those patients with malignancy. Indeed, some patients may benefit more from physiotherapy than others. However, there is a lack of objective criteria to discriminate those who would benefit from physiotherapy. An ongoing study, aims to assess the ability to discriminate between patients who respond to physiotherapy and those who do not (25). Moreover, some factors, such as anaemia, may modify the response to physiotherapy and lead to weakness. A recent study of trauma patients demonstrated a higher level of weakness among patients who received high levels of blood transfusion (26). The current study did not find a relationship between anaemia or neutropaenia and the level of physiotherapy.

#### *Study limitations*

This study has several limitations. First, it is a single-centre study with only 1 physiotherapist treating the patients. Cancer patients are frequently treated in this centre and the goal of care for such patients might be different in another ICU.

Secondly, the level of physiotherapy was decided after a clinical examination. Although, the level recommended depends on the patient's muscular strength and awakening, we could not be sure that subjectivity might have occurred to protect patients from adverse events or failure of physiotherapy sessions.

Thirdly, some patients could not be included in the analysis because their stay in the ICU was short, mostly during a weekend or during a period of non-attendance of the physiotherapist. These missing patient data may have modified the result.

Fourthly, the study did not record the ability of patients to receive cancer treatment after discharge from the ICU. This data is of importance for those patients.

However, the current study was a feasibility study. Moreover, when assessed, the FIM score was not different between non-cancer patients and cancer patients.

Finally, this study could not assess patient-reported outcome and satisfaction. This data remains difficult to assess in the ICU, due to delirium or pain, but it is important to address this in further studies.

## CONCLUSION

Physiotherapy is feasible and safe in cancer patients admitted to ICU who require intubation. Although in this study physiotherapy could be performed on only two-thirds of days in ICU, the results show that intubated cancer patients could receive physiotherapy with a high level of safety. Further research is warranted to explore whether physiotherapy leads to better long-term outcome for these patients, and to further elucidate the barriers to performing physiotherapy in the ICU.

#### *Funding source*

Bourse Le Souffle 2017.

*The authors have no conflicts of interest to declare.*

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