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Research Paper

Bone cement implantation syndrome in patients with cemented endoprostheses for metastatic bone disease in the femur

Thea Hovgaard Ladegaard [a,*], Jakob Stensballe [b,c,d], Michael Mørk Petersen [a,d], Michala Skovlund Sørensen [a,d]

[a] Musculoskeletal Tumor Section, Department of Orthopedic Surgery, Rigshospitalet, University of Copenhagen, Inge Lehmanns Vej 6, 2100 Copenhagen, Denmark
[b] Department of Anesthesiology, Surgery and Trauma Center, Rigshospitalet, University of Copenhagen, Inge Lehmanns Vej 6, 2100 Copenhagen, Denmark
[c] Section for Transfusion Medicine, Capital Region Blood Bank, Rigshospitalet, Inge Lehmanns Vej 6, 2100 Copenhagen, Denmark
[d] Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 33.5, Section A, Copenhagen, Denmark

HIGHLIGHTS

- BCIS occurs in more than 1/3 of patients operated for bone metastases in the femur.
- BCIS incidence did not decrease after increased awareness.
- A multidisciplinary approach may reduce the complications of BCIS.

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ABSTRACT

Background: Patients with bone metastases in the femur (BMf) may experience pathological fractures requiring surgery with cemented endoprostheses (EPR). At cementation and prosthesis insertion, patients are at risk of experiencing hypoxia, hypotension, cardiac failure and potentially death, known as bone cement implantation syndrome (BCIS). We aimed to 1) investigate the incidence and grade of BCIS in patients with BMf treated with cemented EPR, and 2) examine if the incidence or extent of BCIS has decreased after a change of a combined anesthesiologic and surgical protocol.
Methods: We retrospectively assessed patients with BMf operated with cemented EPR in two periods 2017 – 2018 (early cohort) and 2019 – 2020 (late cohort) and stratified before and after the intervention.
Results: Comparing the early and late cohorts, 26/86 (32 %) vs. 30/80 (35 %) experienced BCIS, but mild BCIS (grade 0 + 1) was seen in 79 % vs. 86 %, and severe BCIS (grade 2 + 3) in 21 % vs. 14 %. In the late cohort the per-operative use of vasopressors was higher (86 % vs. 59 %, $p < 0.001$), we found fewer pulmonary embolisms (PE) ($p = 0.024$), and a trend toward a reduced length of stay (LOS). 30-day survival was lower for patients with grade 0 + 1 compared to grade 2 + 3 ($p = 0.03$).
Conclusions: BCIS occurs in more than 1/3 of patients operated for BMf with cemented EPR. An increased multidisciplinary focus on BCIS may reduce the complications of BCIS, such as PE and LOS.

1. Introduction

Persons with bone metastases in the femur (BMf) can experience impending or complete pathological fractures requiring surgery. After the spine, bone metastases most often occur in the femur[1–5] and the surgical options are either to support the bone with internal fixation or a total joint replacement with an endoprosthesis (EPR) or a diaphyseal spacer [1,6].

It is standard procedure and policy to use cemented rather than uncemented implants when treating BMf. In relation to the cementation process and prosthesis insertion, some patients experience hypoxia, hypotension, pulmonary hypertension, arrhythmias, cardiac failure, and eventually cardiac arrest, known as the bone cement implantation syndrome (BCIS)[7,8], which is a well-known and a potentially fatal

* Corresponding author at: Thea Hovgaard Ladegaard, Rigshospitalet, Inge Lehmanns vej 6, 2100 København Ø, Denmark.
E-mail addresses: thea.hovgaard.ladegaard@regionh.dk (T.H. Ladegaard), jakob.stensballe@regionh.dk (J. Stensballe), michael.moerk.petersen@regionh.dk (M.M. Petersen), michala.skovlund.soerensen@regionh.dk (M.S. Sørensen).

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complication of orthopedic surgery involving pressurized bone cement [9]. Several mechanisms have been proposed as the pathophysiology behind BCIS. The most predominant is the role of embolization as a result of high intramedullary pressure during cementation and prosthesis insertion[10], but other mechanisms have been proposed[11–14].

The incidence of BCIS is unclear and has been sparsely described in patients with bone metastases[8]. To our knowledge, only two studies have described the incidence of BCIS in BMf patients[15,16]. The Association of Anaesthetists of Great Britain and Ireland describe in their guideline from 2015 how to reduce the risk of complications during surgery when cementing hemiarthroplasties[17]. They recommend increased awareness of high-risk patients preoperatively, ensuring adequate resuscitation both pre- and intraoperatively and maintenance of vigilance for signs of cardiorespiratory compromise. A randomized controlled trial evaluated the effect of a hemodynamic goal-directed therapy on BCIS in 90 non-cancer patients receiving cemented hip arthroplasties but failed to demonstrate a reduction in the incidence of BCIS. No studies investigating such an intervention on patients treated for BMf exist.[18].

The aim of our study was to 1) investigate the incidence and grade of BCIS and complications in patients treated surgically for BMf with cemented EPR, and 2) to examine if the incidence or extent of BCIS has decreased after the combined change in anesthetic and surgical protocol in 2018. We hypothesized that the incidence or extent of BCIS has decreased in our department after a combined change in anesthesiologic and surgical protocol.

2. Materials and Methods

2.1. Study design

This retrospective study investigated all adult patients (age > 17 years) receiving surgical treatment with cemented EPR due to BMf (proximal, diaphyseal and distal) in two different periods: 1 January 2017 – 31 July 2018 (early cohort) and 1 January 2019 – 31 July 2020 (late cohort) at the Musculoskeletal Tumor Section at Rigshospitalet, a tertiary referral center for orthopedic surgery. Patients with hematological disease (myelomatosis or lymphoma) in the femur were also included since the same surgical strategy was used. In the study period, it was standard procedure and policy at our department to use cemented rather than uncemented implants, why only cemented EPR was included. Further, it is standard procedure at our department for patients to receive general anesthesia in combination with epidural analgesia, when undergoing major hip cancer surgery.

The two cohorts were separated by a 6-month intermediate period to minimize bias in the transition phase after the implementation of the intervention, with the aim of decreasing the number of patients experiencing BCIS. Medical records, operation, and anesthesia charts were reviewed for relevant information on general health status, primary cancer, use of antithrombotic medication preoperatively, implant type, and anesthesia characteristics.

The study was reported according to the STROBE guidelines.

2.2. The change in anesthetic and surgical protocol included

- Infusion of pre-emptive norepinephrine through a Central Venous Catheter (CVC) to increase BP before cementation (goal: systolic BP> 130–140 mmHg) and to support the preload, tonus, and function of the right ventricle, and preparation of standby epinephrine bolus before cementation.
- Goal-directed fluid therapy via Central Venous Oxygen Saturation ($S_{cv}O2$) during surgery.
- Increased oxygen supply by increased Fraction of Inspired Oxygen (FiO2) before cementation.
- No pre-emptive tranexamic acid (TXA), but use of 0.5g of TXA when blood loss exceeds more than 1L, and repeated if blood loss exceeds 2L.
- Specialist in anesthesiology in the operating room during cementation.
- Surgical routine using suction in the marrow channel at cementation and surgical use of venting holes in case of stems surpassing the distal part of the femur.
- Increased focus on thrombosis prophylaxis with Low Molecular Weight Heparin (LMWH) before and especially after the procedure.

In our department, it is standard practice for an anesthesiology specialist to initiate anesthesia at the beginning of the surgical procedure, after which an anesthesia nurse typically takes over and remains in the operating room. However, as part of the new protocol, we have implemented a requirement for an anesthesiology specialist to be present throughout all high-risk procedures, such as cementation, to ensure optimal patient safety. This change aims to enhance intraoperative monitoring and facilitate immediate intervention in case of hemodynamic instability.

2.3. Cementation

The time of cementation was identified from the anesthesia report by either direct mark or note, and when in doubt then two independent physicians (THL and JS) identified the time of cementation, or cementation would be classified as inconclusive, and the patient would be excluded from the study (n=22). When the time of cementation was identified, the use of vasopressors (Norepinephrine, Ephedrine and Phenylephrine), systolic BP, oxygen saturation (SAT) and FiO_2 were registered at four time points: 1) 5 min before cementation, 2) at cementation, 3) 5 min after cementation and 4) 15 min after cementation. Each patient was then classified as having no BCIS (grade 0) or BCIS grade 1–3, according to Donaldson et al.[8]:

- Grade 0: No BCIS
- Grade 1: moderate hypoxia (SpO2 < 94%) or hypotension (fall in systolic BP > 20%)
- Grade 2: severe hypoxia (SpO2 < 88%) or hypotension (fall in systolic BP > 40%) or unexpected loss of consciousness
- Grade 3: cardiovascular collapse requiring cardiovascular resuscitation.

The ratio between SAT and FiO2 (SAT/FiO2) was used as a proxy for the ratio between Partial Arterial Oxygenation (PaO2) and FiO2, to determine how well the patients were oxygenated during cementation.

In the study period, all anesthetic values were monitored routinely by the minute, and all BPs were invasively monitored through arterial cannulation in the radial artery, why we were able to determine the time of cementation precisely.

When patients experience signs of pulmonary embolisms (PE) peroperativly or 30 days postoperatively it is standard procedure at our department to verify the PE diagnosis with transesophageal echocardiography (TEE), computed tomography (CT) of the lungs or pulmonary ventilation/perfusion scintigraphy.

2.4. Statistics

All continuous variables were non-parametric and presented as median with interquartile range or total range when appropriate. Categorical variables were presented as numbers (frequencies). Pearson's Chi-squared test or Fisher's exact test was used for comparison of groups.

The overall probability for survival was calculated by Kaplan-Meier estimates and stratified by time period (early vs. late) and BCIS status (BCIS grade 0+1 vs. BCIS grade 2+3, according to other studies showing similarities in survival between the BCIS grades[7,19]. Differences in survival were assessed by log-rank test. Due to the Danish Civil Registration System, which ensures accurate information on emigration and/or death, we had no loss to follow up.

Confidence intervals (CI) were reported as 95% and p-values <0.05 were considered statistically significant. All statistical analyses were performed in the statistical software R Studio (R Foundation, Vienna, Austria).

3. Results

3.1. Patient demographics

207 patients were eligible for the study. In total, 166 patients were included in the study with primary surgical treatment with cemented EPR due to BMf at our department (Fig. 1). 41 patients were excluded due to revision surgery (e.g. due to previous BMf procedures but also osteoarthritis or traumatically fractures) (n=13), multiple procedures in the same anesthesia (e.g. bilateral hip replacement due to more than one metastasis) (n=4), if treated with intramedullary nails (n=1) and procedures without the use of bone cement (n=1). Further, patients with unknown time of cementation were excluded as well (n=22).

When comparing patients treated in the early (n=80) and late (n=86) cohort, patients were comparable regarding age, sex, type of primary cancer, type of fracture, Karnofsky score preoperatively, extent of primary cancer disease (regarding bone and visceral metastases), history of thromboembolic events and use of antithrombotic medications preoperatively. In the late period, a statistically significantly higher number of patients with ASA group 3+4 were seen (p = 0.012) (Table 1). Patients received hemiarthroplasties in 27 cases (16%) of which 13 were performed with major resection and reconstruction. Total hip replacements were performed in 114 cases (69%) of which 78 were with major resection and reconstruction. A total distal femoral replacement with major resection and reconstruction was performed in 9 cases (5.4%). Sixteen patients (9.6%) received a total hip replacement with partial pelvic replacement due to a metastatic lesion in the acetabula, of which 4 had major resection and reconstruction of the proximal femur as well (Fig. 2). A trend towards a change in the implants used in the early and late cohort was seen, with a larger number of patients receiving a total hip replacement in the late compared to the early cohort (78% vs. 59%, respectively) (p = 0.05) (Table 2).

3.2. BCIS and mortality

The incidence of all grades of BCIS (grade 1–3) was 32% (n=26) in the early cohort and 35% (n=30) in the late cohort, with no statistically significant change between the two cohorts (p=0.7) (Table 3).

Kaplan Meier analysis showed no statistically significant difference between cumulated probability for survival when stratified by patients treated in the early and late cohort. Survival at 30 days and 1 year was 87% (CI 80–95) and 39% (CI 29–50) for the early cohort and 81% (CI 73–90) and 52% (CI 41–62) for the late cohort (Fig. 3a-b). The 30-day survival probability was statistically significantly higher for patients with grade 0+1 than for grade 2+3 (p=0.03). Survival was 87% (CI 81–92) and 72% (CI 56–89) for grade 0+1 and grade 2+3, respectively. However, no change in survival was found 1 year after surgery with 46% (CI 38–54) and 45% (CI 27–62) for grade 0+1 and grade 2+3, respectively (Fig. 4a-b).

3.3. Effect of the combined change in anesthesiologic and surgical protocol

More patients in the late cohort than in the early cohort received vasopressors during cementation (96% vs. 77%, p<0.001) (Table 4), and levels of systolic BP were higher (p=0.04). The median systolic BP were 113 mmHg (95–133 mmHg) and 122 mmHg (112-136mmHg) at

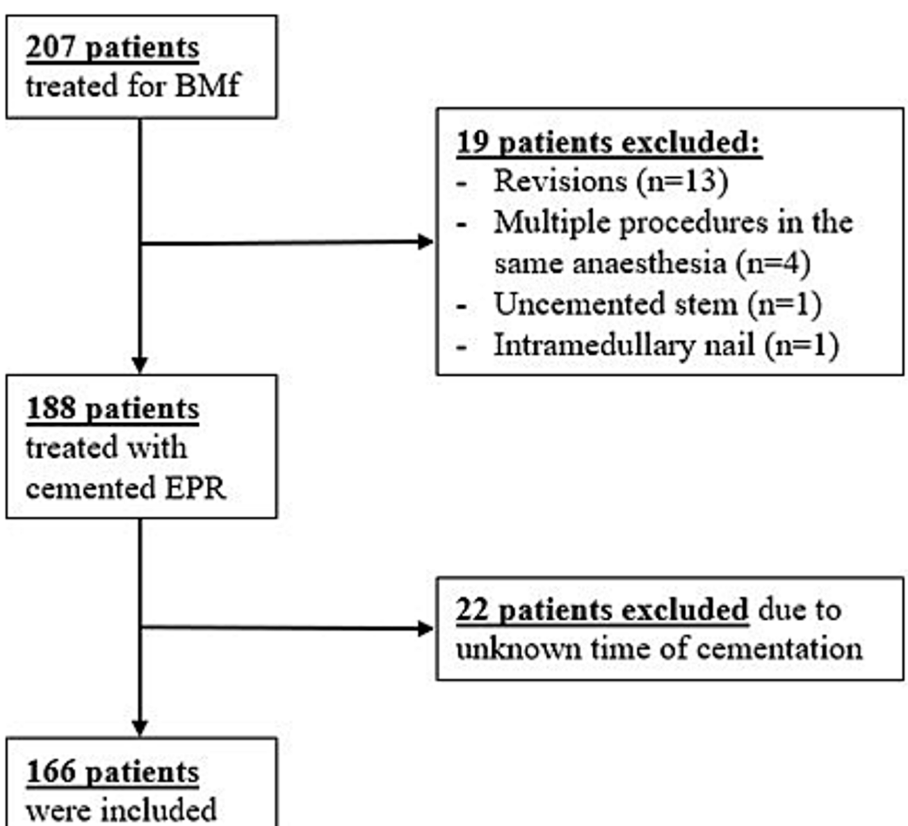

Fig. 1. Flowchart of patients included and excluded.

Table 1
Table describing and comparing the preoperative data of the patients.

Variable	(n/ missing)	Early cohort (n = 80)	Late cohort (n = 86)	p-value
Age (years)	(166/0)	71 (14)	71(14)	0.7[1]
Sex	(166/0)			0.4[2]
Female		42 (52 %)	51 (59 %)	
Male		38 (48 %)	35 (41 %)	
Primary Cancer	(166/0)			0.3[2]
Fast Growth		32 (40 %)	28 (33 %)	
Moderate Growth		27 (34 %)	26 (30 %)	
Slow Growth		21 (26 %)	32 (37 %)	
Fracture	(166/0)			0.8[2]
Complete		58 (72 %)	61 (71 %)	
Impending		22 (28 %)	25 (29 %)	
Karnofsky Score	(166/0)			0.4[2]
<70		13 (16 %)	18 (21 %)	
>=70		67 (84 %)	68 (29 %)	
ASA Group	(166/0)			0.02[2]
Group 1 + 2		22 (28 %)	11 (13 %)	
Group 3 + 4		58 (72 %)	75 (87 %)	
Bone Metastases	(165/1)			0.5[2]
Solitary lesion		22 (28 %)	20 (23 %)	
Multiple lesions		57 (72 %)	66 (77 %)	
Visceral Metastases	(166/0)			0.3[2]
Without/unknown		46 (57 %)	42 (49 %)	
With		34 (42 %)	44 (51 %)	
History of thromboembolic events	(166/0)			0.3[3]
No		75 (94 %)	76 (88 %)	
Yes		5 (6.2 %)	10 (12 %)	
Thrombosis prophylaxis prior to surgery	(166/0)			0.6[2]
No		23 (29 %)	22 (26 %)	
Yes		57 (71 %)	64 (74 %)	

Data are number (%) if not median (interquartile range).
[1] Wilcoxon-Rank-Sum test,
[2] Pearson's Chi-squared test.
[3] Fisher's exact test.

cementation in the early and late cohort, respectively. The median SAT/FiO2 at cementation were 2.2 (1.1–2.9) and 1.4 (1.1–2.5) in the early and late cohort, respectively (p=0.3) (Fig. 5). Statistically significantly fewer patients (0% vs. 6.2%) experienced PE in the late cohort (p=0.02) and a trend toward a reduced length of stay (LOS) was seen from 12 (9) to 9 (7) days (p=0.1).

4. Discussion

The current study showed the effect of a combined change in an anesthesiologic and surgical protocol with more frequent use of vasopressor increasing the BP but no change in the incidence or severity of BCIS was observed. Importantly, PE was fewer, and LOS seemed affected too.

This is somewhat comparable with the results of Yang et al.[16] who

Table 2
Table describing the type of surgery.

Variable	(n/ missing)	Early cohort (n = 80)	Late cohort (n = 86)	p-value
Type of implant	(166/0)			0.05[1]
Hemiarthroplasty		18 (22 %)	9 (19 %)	
Total hip replacement		47 (59 %)	67 (78 %)	
Distal femoral replacement		9 (11 %)	7 (8.1 %)	
Total hip replacement with partial pelvis replacement		6 (7.5 %)	3 (3.5 %)	
Major Bone Resection	(166/0)			0.9[2]
No		30 (38 %)	32 (37 %)	
Yes		50 (62 %)	54 (63 %)	
Stem Length	(166/0)			0.2[2]
< 20 cm		46 (58 %)	57 (66 %)	
>= 20 cm		34 (43 %)	29 (34 %)	

Data are number (%).
[1] Fisher's exact test,
[2] Pearson's Chi-squared test.

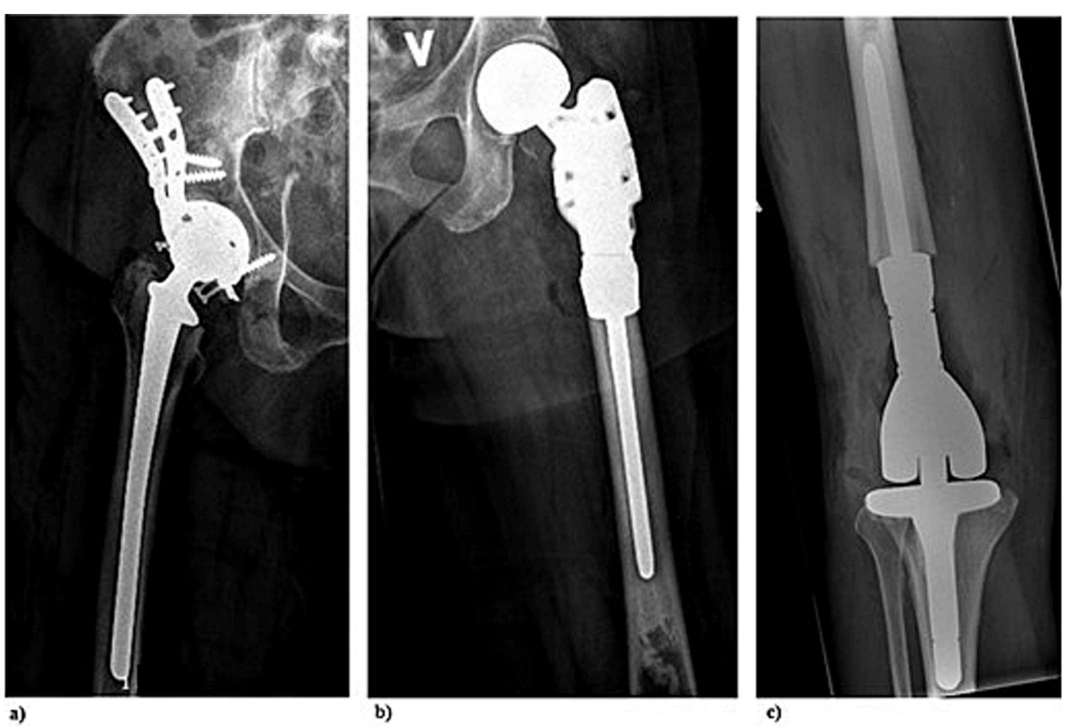

Fig. 2. Examples of surgical implants. a) Conventional total hip replacement (SP2) with partial pelvis replacement (Link Orthopedics UK, Edinburgh, Scotland) (b) Proximal femur resection and reconstruction with tumor prostheses and multipolar head (Segmental System, Zimmer Biomet, Warsaw, IN, USA) c) Distal femur resection and reconstruction with a tumor prosthesis (Segmental System, Zimmer Biomet, Warsaw, IN, USA).

Table 3
Table comparing the effect of the combined anesthesiologic and surgical interventions.

Variable	(n/ missing)	Early cohort (n = 80)	Late cohort (n = 86)	*p*-value
BCIS	(166/0)			0.1[3]
Grade 0		54 (68 %)	56 (65 %)	
Grade 1		9 (11 %)	18 (21 %)	
Grade 2		14 (18 %)	12 (14 %)	
Grade 3		3 (3.8 %)	0 (0 %)	
BCIS	(166/0)			0.2[2]
Grade 0 + 1		63 (79 %)	74 (86 %)	
Grade 2 + 3		17 (21 %)	12 (14 %)	
Pulmonary embolism post-surgery	(166/0)			0.02[3]
No		75 (94 %)	86 (100 %)	
Yes		5 (6.2 %)	0 (0 %)	
Length of stay in hospital post-surgery	(163/3)	12 (9)	9 (7)	0.1[1]
ICU admittance post-surgery	(166/0)			
No		77 (96 %)	85 (99 %)	0.4[3]
Yes		3 (3.8 %)	1 (1.2 %)	

Data are number (%) or median (interquartile range).
[1] Wilcoxon-Rank-Sum test,
[2] Pearson's Chi-squared test,
[3] Fisher's exact test.

found an incidence of 26%, investigating BCIS in 88 patients treated surgically for bone tumors. Contrary, the results of Schwarzkopf et al. [15] found a vastly higher incidence of BCIS at 74% in 374 cancer patients. Part of the explanation for the huge difference in incidence may

Table 4
Table describing the anesthesiologic intervention.

Variable	(n/ missing)	Early cohort (n = 80)	Late cohort (n = 86)	*p*-value
Vasopressors (Norepinephrine or Ephedrine) intraoperatively	(166/0)			<0.001[1]
No		14 (23 %)	3 (3.9 %)	
Yes		47 (77 %)	74 (96 %)	
Epinephrine used at cementation	(166/0)			0.4[2]
No		73 (91 %)	76 (88 %)	
Yes		6 (7.5 %)	10 (12 %)	
Calcium infusion at cementation				
No	(166/0)	76 (95 %)	86 (100 %)	0.05[1]
Yes		4 (5.0 %)	0 (0 %)	

Data are number (%).
[1] Fisher's exact test,
[2] Pearson's chi-squared test.

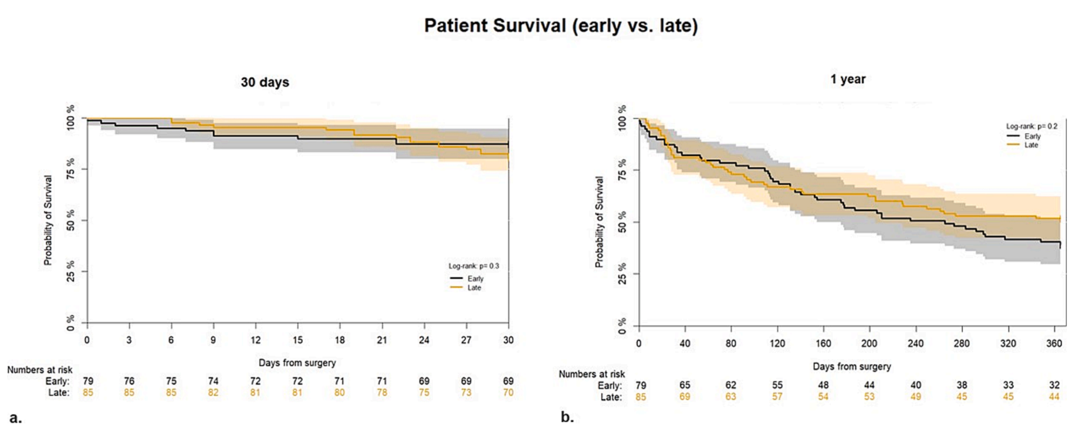

Fig. 3. a-b: Kaplan-Meier analysis illustrating the cumulated probability stratified on the early and late cohorts. **a)** 30-day survival at 87 % (CI 80–95) and 81 % (CI 73–90) (p = 0.3) and **b)** 1-year survival at 39 % (CI 29–50) and 52 % (CI 41–62) (p = 0.2).

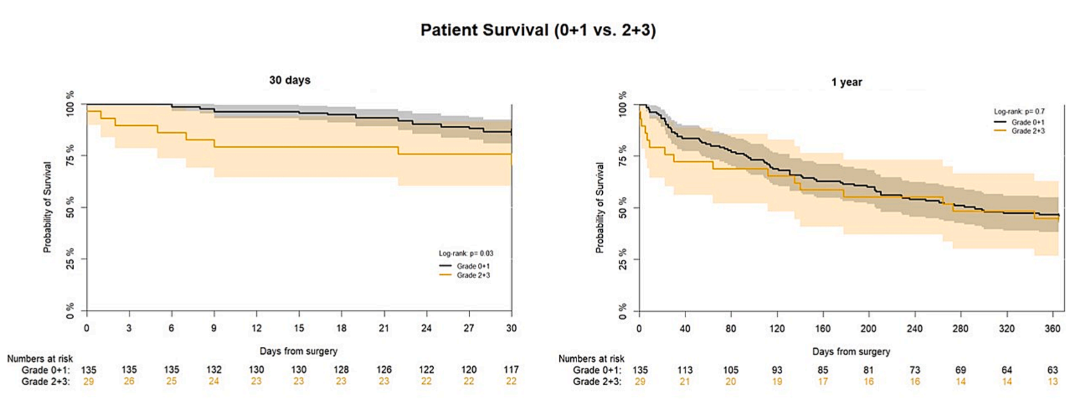

Fig. 4. a-b: Kaplan-Meier analysis illustrating the cumulated probability stratified on grade 0 + 1 and grade 2 + 3. **a)** 30-day survival at 87 % (CI 81–92) and 72 % (CI 56–89) (p = 0.03) and **b)** 1-year survival at 46 % (CI 38–54) and 45 % (CI 27–62) (p = 0.7).

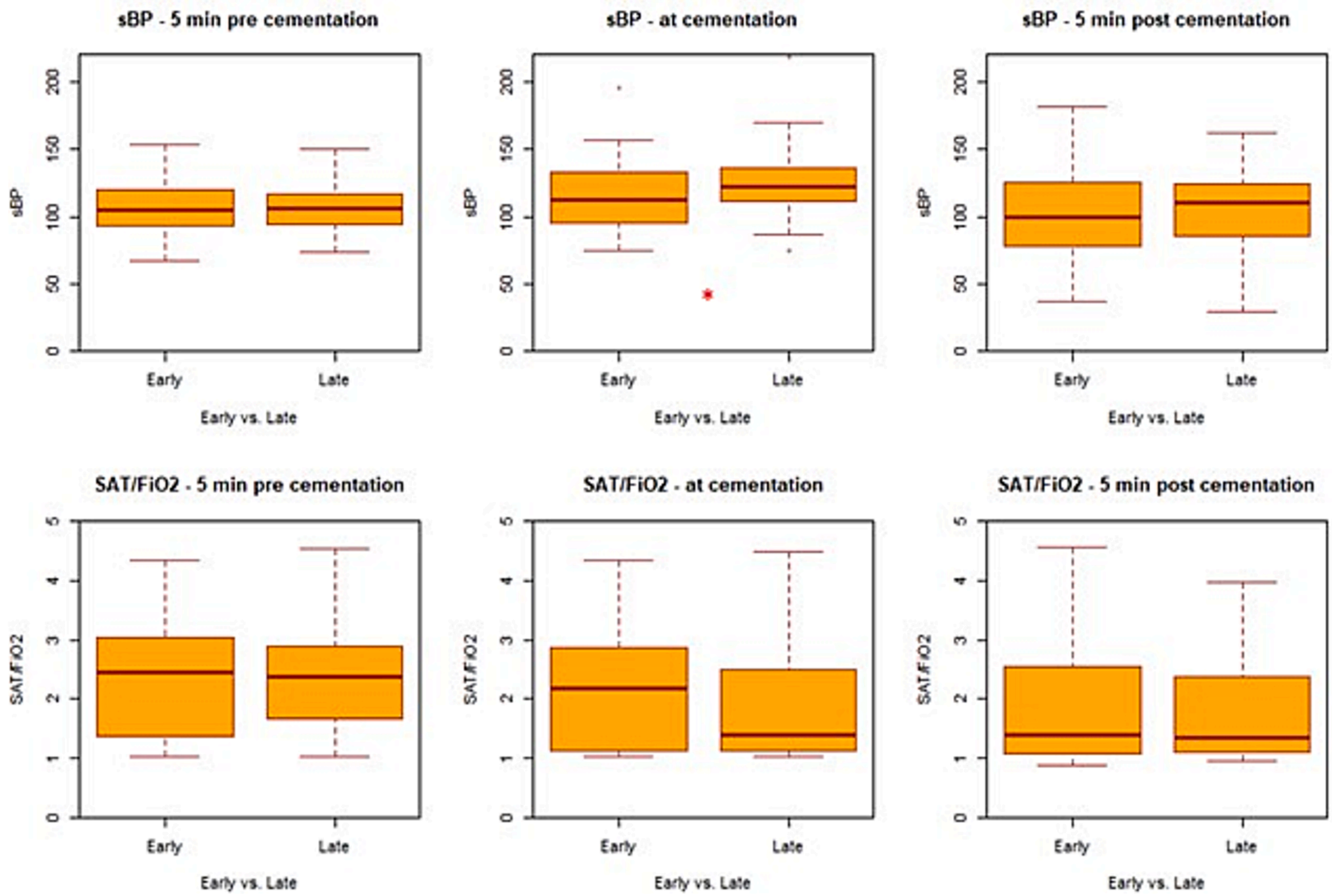

Fig. 5. Box plots illustrating systolic BP and SAT/FiO2 at 3 time points: 5 min before cementation, at cementation and 5 min after cementation for the early and late cohort, respectively. There was a statistically significant difference in systolic BP at cementation between the early and late cohort (p = 0.04). * = statistically significant.

partly be explained by an overestimation of BCIS by Schwarzkopf determining BCIS grade based on BP values from the time of cementation until the end of the post-anesthesia care unit. Oppositely, we only recorded BPs until 15 min after cementation, since BCIS is a phenomenon closely related to the actual cementation process and prosthesis insertion and immediate time after[8].

Given the group of patients with cancer disease often is in a poor general health condition (including low Karnofsky performance score, high ASA group, disseminated disease and pathological fractures) [5,8,20,21] one could expect BCIS to appear more often when surgically treating BMf, compared to patients treated for non-pathological fractures. It has been described that patients undergoing nailing of pathological fractures have more venous endogenic material than those without metastases undergoing hemiarthroplasty, or posttraumatic femoral or tibial intramedullary fixation[22,23]. Further, it has been proposed that cancer patients have increased serious effects of an embolism because the tumor angiogenesis in the metastasis increases local bone vascularity thereby increasing the risk of embolism gaining access to the venous system[24]. There is a well-known association between cancer patients and the risk of venous thrombosis and increased mortality and morbidity[25]. Consequently, the authors of the present study expected to find a higher incidence of BCIS compared to studies reporting BCIS events in non-cancer patients, but interestingly we saw somewhat similar results. Studies investigating BCIS in patients treated with cemented hemiarthroplasties for non-pathological hip fractures or primary repair procedures of the hip found BCIS rates at 37%[26], 35% [27] and 28%[7], and interestingly Price et al.[28] reported cement-associated hypotension in 19% of patients treated with long-stem hip arthroplasties due to bone metastases, reflecting that evidence in the literature is conflicting.

Different risk factors for BCIS are known, including the hypercoagulability state of cancer patients. One study[23] examining both traumatic tibial and femoral fractures and pathological fractures has shown that reamed nailing is associated with the activation of coagulation pathways, intraoperative embolic response, arterial hypoxemia and significant respiratory complications with a more severe response in pathologic fractures. Even though the study of Robinson et al.[23] does not include cemented prostheses, we would expect the more severe responses in cancer patients to be the same for patients undergoing procedures involving bone cement.

Further, we expected a decrease in the incidence and severity of BCIS due to the combined change in anesthetic and surgical protocol. However, no statistically significant change was observed. Likewise, a randomized controlled trial examining an anesthesiologic intervention using hemodynamic goal-directed therapy to prevent BCIS in non-pathological hip fractures did not find any statistically significant changes in the incidence of BCIS[18], similar to our results. However, our study and the RCT are limited due to the small sample size.

The continuously high incidence of BCIS in this patient cohort even after the implementation of anesthetic and surgical precautions highlights the need for continued awareness of this non-rare condition in patients treated surgically for BMf. The Association of Anaesthetists of Great Britain and Ireland (ASAP) guidelines[17] recommend adequate resuscitation both pre- and intraoperatively, optimal oxygenation and ventilation, and maintenance of vigilance for signs of cardiorespiratory collapse. Further, some studies have suggested that the type of anesthesia, particularly neuraxial anesthesia, may be associated with the risk of developing BCIS[29,30], while others find no coherence with type of anesthesia and postoperative survival [31]. The improved focus on the development of BCIS in high-risk cancer patients at our department may have led to no patients experiencing BCIS grade 3 in the late cohort. The greater focus is reflected in the increased use of vasopressors in the late cohort, resulting in increased BP levels during cementation, and an enhanced focus on well-oxygenated patients and maintenance of normovolaemia, pre-, under- and post-cementation.

Survival rates in patients with bone metastases have been investigated in several studies. Reviewing the literature, the probability of overall survival is 29% – 51% 1 year after surgery[3,32–40]. The present study found similar survival rates in patients with mild and severe BCIS after 1 year, but short-term survival 30 days post-surgery was statistically significantly lower for patients with severe BCIS, indicating that despite the measures to avoid hypoxia, hypotension and cardiac failure we are still challenged. This is in line with the findings of Rassir et al. [19] reporting poorer 30-day survival for patients experiencing severe grades of BCIS, but contradicting the findings of Jaffe et al.[27], finding no coherence with 30-day mortality and severeness of BCIS, which might be due to the small sample size of only 90 patients, thus an underpowered study.

When assessing the risk of developing venous thromboembolisms, patients receiving hip or knee arthroplasties are in the high-risk group [41] and adding to the risk is the presence of cancer. Patients with disseminated cancer, who undergo surgical procedures, especially orthopedic procedures in the lower extremities, are more likely to experience fatal PE than patients without cancer undergoing a similar procedure[42].

Despite the lack of change in the incidence or severity of BCIS in the two cohorts, we observed a statistically significant change in the number of PE from 6.2% to 0% ($p=0.02$). One could expect the explanation to be an increased focus on preoperative thromboprophylaxis, but we failed to demonstrate such a difference between the two cohorts. Information on postoperative thromboprophylaxis would have been preferred, as a possibly more aggressive use in the late cohort might have influenced the number of patients experiencing PE. When it comes to the anesthesiologic and surgical risk for these patients, are we measuring what is clinically most important for decreasing fatal events such as PE, by using the BCIS grading system, which has never been validated in a clinical setting. One could argue that current BCIS definitions and grading systems need further validation, supporting further research in this field.

The present study does have some limitations. A major limitation is a retrospective design impeding accurate decisions about the time of cementation if not mentioned in the anesthesia charts, resulting in the exclusion of 22 patients. Further, 28 patients were grouped as having no BCIS (flat line on anesthesia charts), resulting in missing data regarding the information on BP, SAT, FiO2 and the use of vasopressors intraoperatively.

While efforts were made to assess adherence to the established protocol in the late cohort, some details – such as the use of suction and venting holes and the presence of an anesthesia specialist – were not consistently documented in the patient files. Consequently, these specific factors could not be included in the analysis. However, all available data related to protocol adherence have been transparently reported in the tables, with missing information acknowledged.

Another potential limitation is that patients were grouped into two cohorts based on time periods, raising concerns that unmeasured changes in clinical practice may have influenced the results. However, apart from the implementation of the new protocol under investigation, no major changes in surgical techniques, anesthesia management, or perioperative care occurred during the study period. The same group of surgeons performed all procedures, and patients in both cohorts were comparable in all baseline characteristics except for ASA score. While minor variations in clinical decision-making over time cannot be entirely ruled out, the consistency in practice and patient characteristics helps minimize the risk of bias related to temporal changes.

In addition, the small number of patients experiencing severe grades of BCIS (only 3 patients with grade 3 in the early and 0 in the late cohort), limits the ability to conclude on minor changes in the incidence of BCIS between the two cohorts, according to current BCIS definitions, why the study is probably underpowered. Further, the cohort comprises all kinds of cemented EPR, including different stem lengths and patients with metastases in the acetabular area, proximal, and distal femur, why the heterogeneity makes the results inherent to bias.

The advantages are our ability to find all relevant signs of BCIS in precisely noted anesthesia charts, monitored by the minute for all included patients during the entire study period. Further, all patients were surgically treated in the same department by the same few tumor surgeons and anesthesiologists with the same general treatment recommendations and precautions in mind.

Nevertheless, the heterogeneity of the patient population remains a potential source of bias that could confound the results. Future larger studies should consider stratifying analyses by subgroups to understand variations in BCIS outcomes better and improve risk assessment. Identifying specific risk factors for BCIS is crucial to improve patient selection for surgical treatments, and to enable both surgeons and anesthesiologists to take necessary precautions preoperatively and intraoperatively to mitigate BCIS risk. Randomized controlled trials are always the gold standard, but the ethical considerations for this group of patients with often very short life expectancies and the need for individual treatment allocation, make those studies difficult to conduct.

5. Conclusions

BCIS is an event occurring in more than 1/3 of patients operated for bone metastases in the femur with cemented endoprostheses. Our study showed that an increased multidisciplinary focus on this phenomenon may reduce the complications of BCIS such as pulmonary embolism and hospital stay.

The study highlights the continued need to understand and prevent BCIS in patients with bone metastases in the femur. An increased multidisciplinary focus including pre- and intraoperative anesthetic measurements and surgical precautions may aid in improving the outcome and short-term survival for patients experiencing BCIS. However, given the low number of severe BCIS cases in our cohorts, the study may be underpowered to detect small but clinically significant differences. Additionally, due to the lack of randomization, it cannot be stated with certainty that there is an equal distribution of risk factors between the early and late cohorts. As such, this study may serve as a pilot for future, larger studies to further explore the impact of multidisciplinary strategies in managing BCIS.

7. Author Statement

All authors have made substantial contributions to the study and have approved the final revised version of the manuscript. Specific contributions are as follows:

Study concepts and design: THL, JS, MMP, MSS.
Data acquisition: THL, MSS.
Quality control of data and algorithms: THL.
Data analysis and interpretation: THL, JS.
Statistical analysis: THL.
Manuscript preparation: THL.
Manuscript editing: THL, JS, MMP, MSS.
Manuscript review: THL, JS, MMP, MSS.

CRediT authorship contribution statement

Thea Hovgaard Ladegaard: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jakob Stensballe:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology, Conceptualization. **Michael Mørk Petersen:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Michala Skovlund Sørensen:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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