Single-Stage versus Two-Stage Intramedullary Nailing for Synchronous Impending or Pathologic Fractures of Bilateral Femur for Oncologic Indications: A Systematic Review of Outcomes

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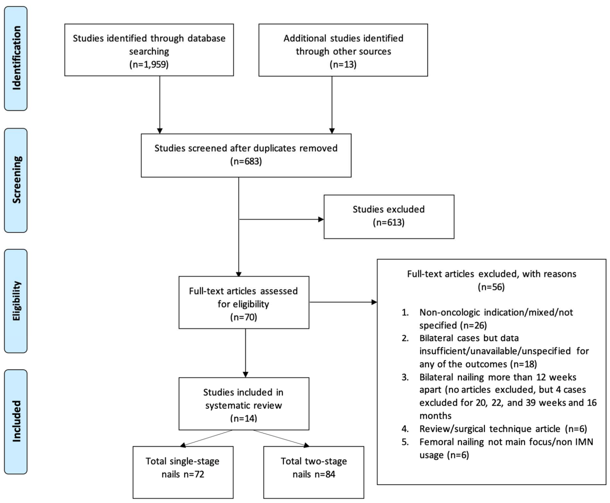
INTRODUCTION: Intramedullary nail (IMN) fixation is a common surgical treatment for patients with metastatic bone disease of the femur. Multiple synchronous impending and/or complete pathologic long-bone fractures may be present in patients with advanced metastatic disease. Single-stage multiple IMN raises concern of increased complications and mortality, especially with bilateral femora. However, advantages include single anesthesia, expedited mobilization, early start of adjuvants, reduced length of stay, and decreased overall cost. Although few recent studies have shown encouraging results, they are limited by their study design, and thus the optimal surgical timing (single- vs. two-stage) remains controversial. Therefore, the objective of this study was to conduct a systematic review of the existing literature regarding the outcomes after single-stage and two-stage IMN fixation of bilateral femora for oncologic indications.

METHODS: The literature search was conducted based on the PRISMA guidelines. We queried four electronic databases (Medline/PubMed, EMBASE, Scopus, and the Web of Science) up to February 2023. Eligible studies reporting on outcomes of single-stage vs. two-stage bilateral femoral IMN procedures in patients with synchronous pathologic or impending fractures, were included. Studies were excluded if IMN was done for non-oncologic indications, metachronous bilateral femur disease, and/or IMNs performed during different admissions (defined as > 12 weeks), insufficient or not available data, non-IMN fixation methods (e.g., arthroplasty, plating, or tumor prosthesis), and if details regarding staging/timing and outcomes were unspecified. The information (if reported) retrieved from each publication included: 1) general study information (e.g., author, title, study design, year of publication); 2) single-stage vs. two-stage; 3) patient demographics (e.g., age, sex, primary tumor, etc.); 4) details of the surgical procedure; and 5) outcome measures of patient safety (medical and surgical complications), efficacy (implant related complications), and survival.

RESULTS: Out of 70 articles screened from original 1,972 publications, only 14 eligible studies met inclusion criteria. These studies reported on 156 IMN inserted in 78 patients. Thirty-six (46.2%) patients underwent single-stage bilateral IMN fixation, and 42 (53.8%) patients underwent a two-stage procedure. Measures of patient safety (medical and surgical complications) were reported in 9 publications for 34 in the single-stage and 24 patients in two-stage group. Total complications were reported in 5 of 34 (14.7%) in the single-stage and 11 of 24 (45.8%) patients in the two-stage group (p=0.021) and were mostly medical complications [5 (14.7%) vs. 10 (41.6%); p=0.045]. In the single-stage group, all 5 medical complications were cardiopulmonary in nature. Four were intraoperative and occurred during insertion of the second IMN. These included three cardiac arrests associated with fat/tumor/pulmonary emboli (1 intraoperative death and two successfully resuscitated [one survived 5 months and other alive at last follow up at 7 weeks]), and one case of hypotension requiring resuscitation. One case of respiratory distress occurred in the recovery room from presumed fat emboli (died day 15). In the two-stage group, 7 patients had cardiopulmonary complications. Three were intraoperative (2 cardiac arrests leading to death secondary to air/fat emboli and 1 intraoperative hypotension requiring resuscitation), and 4 were postoperative (one each of pleural effusion, pneumonia, respiratory distress, pulmonary embolism leading to multiorgan failure. Three more patients had postoperative renal complications (2 urinary tract infection and 1 acute renal failure). There were no surgical complications in the single-stage but 1 (4.2%) deep wound infection requiring surgical debridement occurred in the two-stage group (p=0.86). Measures of efficacy, specifically implant failure, were reported as none in 6 studies for 13 and 34 patients in the single-stage and two-stage groups, respectively. Survival data was available for 25 and 19 patients in the single-stage and two-stage groups respectively. Of these, 15 (60.0%) and 14 (73.7%) patients survived 30 days or longer (p=0.530), and 14 (56.0%) and 10 (52.6%) patients survived 90 days or longer (p=1.000), in the single-stage and two-stage subgroup, respectively.

DISCUSSION AND CONCLUSION: Our systematic review supports a single-stage IMN approach as a comparable treatment strategy for select patients with synchronous bilateral pathologic impending or complete femoral fractures. While medical complications rates were higher in two-stage IMN, this could represent selection bias due to sicker patients and reporting bias as postoperative complications were not reported in all but one study. Compared to studies in the 1990s to early 2000s, more recent studies seem to report more favorable complication rates and survivorship, suggesting advancements in management strategies. Despite our study being the largest and most comprehensive of its kind, research on this topic is limited, underpowered, and often has intrinsic selection bias and insufficient data, and thus future investigations with higher levels of evidence and larger sample sizes are warranted to determine an optimal treatment protocol for this increasingly prevalent clinical situation.


Identification
Screening
Eligibility
Included
Studies identified through database searching (n=1,959)
Additional studies identified through other sources (n=13)
Studies screened after duplicates removed (n=683)
Studies excluded (n=613)
Full-text articles assessed for eligibility (n=70)
Full-text articles excluded, with reasons (n=56)
1. Non-oncologic indication/mixed/not specified (n=26)
2. Bilateral cases but data insufficient/unavailable/unspecified for any of the outcomes (n=18)
3. Bilateral nailing more than 12 weeks apart (no articles excluded, but 4 cases excluded for 20, 22, and 39 weeks and 16 months
4. Review/surgical technique article (n=6)
5. Femoral nailing not main focus/non IMN usage (n=6)
Studies included in systematic review (n=14)
Total single-stage nails n=72
Total two-stage nails n=84

Author (Year)	Level of Evidence	Single-stage vs. Two-stage	Number of Patients (n)	Sex (M:F)	Mean age (range)	Type of nail (n)	Nail size	Canal venting (n)	Reamed vs. unreamed (n)	Time delay before 2nd procedure, n	Primary tumor type (n)	Fracture /lesion location (n)	Pathologic fracture (n)	Impending fracture (n)	Duration of follow-up, month (range)	Implant Failure	Medical and Surgical Complications, n	Mean survival after final surgery, months	Mortality (%)
Kerr *et al.* (1993)	IV	Single-stage	1	0:1	51	AO nail - 1		No	Reamed - 1		Breast - 1	Multiple	0	1			Intraoperative cardiac arrest – 1 (1 fat embolism)	5	
		Two-stage	2	0:2	64.5 (61-68)	Reconstruction nail - 2		Distal venting - 1	Reamed - 2	9 days - 1 12 days - 1	Breast - 2	Multiple	0	1			Intraoperative cardiac arrest – 2 (1 air/1 fat emboli)	0	Intraoperatively - 100
Damron *et al.* (1999)	IV	Single-stage	1			Long Gamma nail - 1 All patients in this series had 130-degree implants placed	17mm proximal diameter 11mm distal diameter		Reamed - 1		Unknown primary - 1 Prostate - 1		0	1		None			
		Two-stage	1			Long Gamma nail - 1 All patients in this series had 130-degree implants placed	17mm proximal diameter 11mm distal diameter		Reamed - 1				0	1		None			
Giannoudis *et al.* (1999)	IV	Single-stage	3	1:2	58.67 (51-69)	AO solid nail - 3	9mm nail		Unreamed - 3		Breast - 2 Lung - 1	Proximal - 4 Middle - 2 Distal - 0	6	0	4.67 (3-6)	None	ARDS - 0		
		Two-stage	0																
Assal *et al.* (2000)	IV	Single-stage	0														None		
		Two-stage	2						Unreamed – 2	2 weeks – 1 3 weeks – 1							None		
Barwood *et al.* (2000)	IV	Single-stage	0																
		Two-stage	1	0:1						3 days - 1									
Cole *et al.* (2000)	III	Single-stage	1		52	AO solid nail - 2		No	Reamed - 1		Prostate - 1		First nail - 1 Second nail - 1			None		28 weeks	
		Two-stage	4		70.71			No	Reamed - 2 Unreamed - 2	Average: 20.75 days Pt. 1 - 6 days Pt. 2 - 10 days Pt. 3 - 11 days Pt. 4 – 56 days	Breast - 1 Prostate - 1 Myeloma - 1 Unknown - 1		First nail - 3 Second nail - 1	First nail - 1 Second nail - 3		None		Pt. 1 – 5 weeks Pt. 2 – 3 weeks Pt. 3 – 8 weeks Pt. 4 – 3 weeks	
Gibbons *et al.* (2000)	III	Single-stage	0			Long Gamma nail - 4 AO solid nail - 3													
		Two-stage	7					No	Reamed - 4 Unreamed - 3				0	7		None			
Edwards *et al.* (2001)	IV	Single-stage	1	0:1		Long Gamma nail - 1			Reamed - 1		Breast - 1		0	1			Intraoperative pulmonary embolism leading to cardiac arrest	0	Intraoperatively - 100
		Two-stage	0																
Samsani *et al.* (2003)	IV	Single-stage	0																
		Two-stage	3	0:3		Long Gamma nail - 3 130-degree cephalic screw	11 or 12mm		Reamed - 3	2-3 weeks	Breast - 3	Subtrochanteric							
Ristevski *et al.* (2009)	III	Single-stage	Total - 18 Fracture - 8 Prophylactic treatment - 3 Combination - 7	Fracture - 2:6 Prophylactic treatment - 1:2 Combination - 2:5	Fracture - 65.8 Prophylactic treatment - 67.5 Combination - 60.8	N/A	N/A	N/A	N/A		Fracture: Lung -1 Breast - 3 Other - 4 Prophylactic: Prostate -1 Other - 2 Combination: Lung - 3 Breast - 1 Other - 3	Diaphyseal	15	10			DVT within 3 months: Fracture - 0 Prophylactic - 0 Combination - 0	Fracture:‡ Intraoperatively - 2 Admission - 3 3 months - 4 Prophylactic:‡ Intraoperatively - 0 Admission - 0 3 months - 0 Combination:‡ Intraoperatively - 1 Admission - 2 3 months - 3	Fracture: Intraoperatively - 25 Admission - 37.5 3-month - 50 Prophylactic: Intraoperatively - 0 Admission - 0 3-month - 0 Combination: Intraoperatively - 14.3 Admission - 28.6 3-month - 42.9
		Two-stage	0																
Moon *et al.* (2011)	IV	Single-stage	2	2:0	63 (58-68)				Reamed - 2		Urothelial - 1 Esophageal - 1	NS	0	2			Postoperative respiratory distress from presumed fat emboli - 1	2 weeks – 1 > 4 weeks – 1	
		Two-stage	0																
Shemesh *et al.* (2014)	IV	Single-stage	1	0:1	67						Breast - 1	Pertrochanteric - 1 Subtrochanteric - 1	1	1		None		18	
		Two-stage	1	0:1	64					2 weeks	Breast - 1	Pertrochanteric /Subtrochanteric - 1 Pertrochanteric - 1		2		None	Infection that required debridement	11	
Fujita *et al.* (2018)	IV	Single-stage	1	0:1	64				Reamed – 1		Breast – 1	Subtrochanteric – 1	1	0			Intraoperative cardiac arrest due to primary tumor/fat embolism with successful resuscitation		
		Two-stage	0																
Maheshwari *et al.* (2023)	III	Single-stage	7	2:5	57.6 (32-76)	Gamma 3, Stryker Trauma GmbH, Schönkirchen, Germany or TFNA, Depuy-Synthes GmbH, Oberdorf, Switzerland)	10	no	Diaphyseal reaming was avoided/minimized and only done when the canal was narrow.		MM - 3 Breast – 2 Granular Cell Sarcoma – 1 Lung – 1	Multiple	1	6		None	Hypotension - 1	662 days - 1	
		Two-stage	21	11:10	65.7 (42-84)		10	no		Average: 7.05 days (n=21)	MM – 10 Thyroid – 1 Breast – 3 Lung – 3 Prostate – 4	Multiple	5 (4 of which were mixed pathologic/impending)	16		None	Bilateral pleural effusion - 1 Hypotension – 1 Respiratory distress – 1 PE, multi organ failure due to POD -1 Pneumonia – 1 Urinary tract obstruction and UTI -1 AKI – 1 UTI - 1	Average: 385.8 days (21-1138) (n=10)	No intraoperative deaths. Excluding those lost to follow up (n=12): 30 days – 8.3 90 days – 25.0 365 – 50.0

POD: progression of disease
PE: Pulmonary embolism
AKI: Acute kidney injury:
UTI: urinary tract infection
ARDS: Acute Respiratory Distress Syndrome
MM: Multiple Myeloma