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POLY-METHYL-METACRYLATE DOES NOT PROVIDE SIGNIFICANT REINFORCEMENT TO A CADAVERIC DIAPHYSEAL MODEL UNDERGOING BENDING STRESS

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1. INTERVENTIONAL RADIOLOGY MANAGMENT OF BONE METASTASTIC DISEASE

Different percutaneous image-guided techniques can be used for the curative and palliative treatment of bone metastases. Such techniques are commonly distinguished into "ablative" and "consolidative".

Ablative techniques are applied to achieve partial or complete tumoral necrosis by dramatic intra-tumoral temperature increase (≥ 55°C) or decrease (around -140°C) [1].

Consolidative treatments aim at obtaining bone defect reinforcement in order to prevent or stabilize non-displaced or minimally displaced pathologic/bone insufficiency fractures. Different consolidative techniques are available based on the specific bone concerned by the target lesion. In particular, in bones where compressive stresses are predominant (e.g. vertebral body, acetabular roof, etc.), percutaneous injection of poly-methyl-methacrylate (PMMA) cement (i.e. cementoplasty or osteoplasty) is commonly used to achieve adequate pain and fracture risk management; on the other hand, in bones were torsional or bending stresses are involved (e.g. pelvic ring, long bones), PMMA alone seems a suboptimal consolidative method thus, often requiring combination with other surgical or non-surgical techniques (e.g. endomedullary nailing, screws, etc.) [2,3].

Interventional radiology strategies and techniques applied to treat bone metastases are herein presented; and the quality of the evidence supporting their application is provided according to the Scottish Intercollegiate Guidelines Network *(SIGN)* [4].

1.1 Strategies for interventional radiology (IR) management of bone metastases

According to the guidelines published by the Cardiovascular and Interventional Radiological Society of Europe for bone tumor management [5], before approaching a bone tumor, it should be clear whether:

1) the goal of treatment is "curative" or "palliative"
2) the target lesion (and the interventional treatment planned) confers to the target bone a substantial risk of fracture

1.2 Curative treatment

- *Indications*

The goal of curative treatments is to completely destroy the target tumor with a safety margin of 5-10 mm of normal surrounding tissue in order to maximize the curative effect of the treatment by preventing local recurrences.

This therapeutic option is reserved to few selected patients presenting with limited bone disease (< 3 potentially treatable bone metastases, each sized ≤ 3 cm), especially if they are young, affected by slow-evolving cancers and without extra-bone metastatic disease.

Curative treatments are achieved with percutaneous thermal ablation performed with radiofrequency ablation (RFA), microwave ablation (MWA) or, more often cryo-ablation (CA).

- *Available evidence*

Deschamps et al retrospectively reviewed their clinical experience with percutaneous ablation of 122 bone metastases (74 treated with RFA and 48 with CA) from several different primary cancers in 89 patients [6]; 38 tumors required additional cementoplasty following ablation. Definition of "curative treatment" was composite as they distinguished their population in two groups: in the first one, the goal was to achieve complete treatment of all bone metastases; in the second one, the goal was focused on prevention of skeletal related events (SREs). Criteria applied for evaluation of treatment failure were: increase ≥ 5% of the bone metastasis diameter as compared to baseline imaging and/or evidence of residual tumor uptake as depicted at enhanced CT, MR and/or PET-CT along follow-up (mean 22.8 months). Factors associated with reduced risk of treatment failure were: bone metastasis metachronous to the primary cancer, absence of cortical bone erosion, maximum lesion diameter <20 mm, absence of critical neurological structures near the target tumor and metastases belonging to the first group of patients. Major complications (grade 3 according to the NCI CTC-AE V4) were noted in 3% cases (i.e. avascular necrosis of the femoral head after thermal ablation of a peri-acetabular lesion; nerve root injury in 2 cases; and transient stress cardiomyopathy after ablation of a bone metastasis from pheochromocytoma).

Seven patients (8%) experienced SREs following thermal ablation. SREs were mainly consistent with long bones fractures occurring at the treated site. Most of the fractures required surgical fixation (n=6; mean interval 44 days; range 12-181). The remaining SRE was consistent with spinal cord compression 8 months after failure to treat a thoracic spinal metastasis.

McMenomy et al retrospectively reported their experience with CA applied to achieve complete disease remission in 40 patients affected by bone and soft tissue metastases from several different primary cancers [7]. Regarding bone metastases, they treated 19 lesions (median tumor size 20mm); additional cementoplasty was needed in two weight-bearing areas (one acetabulum and one vertebral body).

Treatment failure was determined according to the following criteria: diameter increase of the lesion as compared to baseline imaging and/or evidence of tumor uptake at enhanced CT, MR and/or PET-CT along follow-up. Local tumor control was achieved in 13/19 (68%) treated bone lesions. In the whole population, including both bone and soft tissue metastases, 1- and 2-years disease-free survival rates were 22% and 7%, respectively. Median disease-free survival was 7 months.

One major complication (grade 3 according to the NCI CTC-AE V4) was noted (i.e. avascular necrosis of the femoral head after thermal ablation of a peri-acetabular lesion).

Unfortunately, to the best of our knowledge, there are no studies analyzing the feasibility, safety and efficacy of the MWA in the curative setting.

Evidences to apply percutaneous ablative treatments with curative intents are low (SIGN 3) due to substantial absence of prospective randomized controlled trials.

1.2 Palliative treatment (thermal ablation)

- *Indications*

The goal of palliative treatments is not to radically destroy the tumor but: a) to alleviate pain; b) to prevent SRE's (especially fractures) by destroying bone tumor deposits and/or consolidating bones presenting with an impending fracture due to a metastatic lesion, or a pathologic non-displaced/minimally displaced fracture.

This therapeutic option is recommended for patients with at least moderate (≥ 4 in a 0-10 point visual analogue scale, VAS, in a 24-hour period) and focal pain, an impending fracture in a weight-bearing area or a painful pathologic fracture.

Palliation should always be performed following a correlation between patients' clinical and imaging findings.

Palliative treatment can be achieved with percutaneous consolidative techniques alone (e.g. cementoplasty, screw fixation) or in combination with thermal ablation techniques (i.e. RFA, MWA, CA or High Intensity Focused Ultrasound, HIFU).

Ablation is applied to treat pain correlated to one or few bone metastatic foci as confirmed by clinical and radiological findings. In such cases, ablation should be targeted on the most aggressive part of the tumor, which corresponds to the interface between normal bone and neoplastic tissue.

- *Available evidence*

A single-arm prospective trial ("Multicenter American College of Radiology Imaging Network Trial" [8]) proved that RFA safely achieves pain palliation caused by bone metastases. Fifty-five patients with pathologically confirmed malignant disease presenting with a painful (>50 on a 1-100 scale despite analgesic medications) bone metastatic lesion were treated. Patients with primary hematological malignant diseases, lesions ≥ 9cm, or involving weight-bearing bones of the lower limbs or invading the spinal canal or infiltrating nerve roots were excluded. Admitted associated treatments were: previous treatment with bisphosphonates, radionuclide or external beam radiation therapy stopped >1 month before ablation; chemotherapy stopped >2 weeks before ablation and restarted >2 weeks after ablation. Target intra-tumoral temperature >60°C was considered as an indicator of adequate ablation. Mean tumor size was 52 mm.

Three grade 3 toxicities (according to the NCI CTC-AE V4 classification) were reported (i.e. refractory pain and neural damage). Investigated variables were "pain relief", "patients' mood" and "pain intensity" at 1- and 3-months follow-up based on a 0-100 point-scale. At the same time intervals, also "pain severity" was evaluated on a dedicated 1-8 scale (1= no pain; 8= excruciating pain).

Average increase in pain relief from pre- to post-ablation was 26.3 ($p < 0.0001$) and 16.4 ($p=0.02$) at 1- and 3-months follow-up, respectively. The average increase in patients' mood from pre- to post-ablation was 19.9 ($p <0.0001$) and 14.9 ($p=0.005$) at 1- and 3-months follow-up, respectively. The average decrease in pain intensity from pre- to post-ablation was 26.9 ($p <0.0001$) and 14.2 ($p=0.02$) at 1- and 3-months follow-up, respectively. In the end, the odds of being in lower pain severity at 1-month follow-up were 14.0 ($p < 0.0001$) times higher than at pre-ablation; the same odds at 3-month follow-up were 8.0 ($p < 0.001$) times higher than at pre-ablation. None of the outcomes correlated with the volume of ablation or with previous radiotherapy to the same site treated with RFA.

Callstrom et al carried out a single-arm, observational, multicenter trial [9] proving that percutaneous CA is a safe therapeutic option to achieve pain palliation in patients with bone metastases. They treated 61 patients with limited painful bone metastases (1 or 2 painful lesions according to a 0-10 VAS score ≥ 4 over 24 hours). Chemotherapy or radiation therapy were stopped >3 weeks prior to the enrollment in the study. Response to ablation was evaluated with the Brief Pain Inventory-Short Form. Evaluation of analgesic drugs consumption was also recorded. In the whole, 69 tumors (mean size 48 mm) were treated. The mean score for worst pain in a 24-hour period passed from 7.1/10 before ablation to 5.1/10, 4.0/10, 3.6/10, and 1.4/10 at 1-, 4-, 8-, and 24-weeks follow-up, respectively; 83% patients needing opioid intake before CA reduced it along follow-up. One major complication (grade 3 according to the NCI CTC-AE V4) consistent with an infection in the treated area was noted.

Palliation of bone metastases achieved with HIFU was reported by Gianfelice et al. [10]. They treated with MR-guided HIFU, under conscious sedation, 11 patients affected by painful localized bone metastases. Most of the treated lesions were osteolytic (n = 8); few osteoblastic (n= 2) and one mixed (n= 1). Average VAS scores before treatment was 6.0 (range, 4–9); and it decreased to a mean score of 1.3 and 0.5 at 1- and 3-month follow-up, respectively. All patients diminished their intake of analgesic drugs; 7 patients no longer needed any pain medication at 3-month follow-up and the remaining 4 patients decreased the dose of analgesic by at least 50%.

No complications were noted during the entire follow-up (3 months). The majority of patients affected by osteolytic metastases showed a certain extent of necrosis in the enhancing medullary component of the lesion at 1- and 3-month follow-up obtained by means of contrast-enhanced MR imaging. Interestingly, at 3-month CT follow-up, 56% osteolytic lesions showed an increased bone density thus, suggesting a potential consolidative role of HIFU. However, this hypothesis needs to be confirmed by further investigations. A further and larger study conducted in 31 patients supported the use of HIFU in treating painful bone metastases [11]: 25 patients completed the 3-month

follow-up with a mean VAS score of 1.8 (vs 5.9 before treatment). Reduction of opioid intake was reported in 67% patients. Also in this study no adverse events were noted.
Although promising, palliative results obtained with MWA are still very limited [12, 13]. Therefore, larger prospective studies are needed to confirm the safety and effective profile of MWA in the palliative setting.

Evidences obtained from single-arm prospective multicenter studies strongly support ablative techniques (RFA, CA, HIFU) applied to alleviate pain caused by bone metastases (SIGN2+). Further prospective studies are needed to investigate the performance of MWA.

1.3 Palliative treatment (consolidation)

- *Indications*

All bone metastases should be evaluated in order to find out impending or pathological fractures especially in weight bearing bones. The same evaluation should be considered following bone curative or palliative ablation since bone is weakened by the ablation thus, potentially being at risk for secondary stress fracture.
Basic qualitative parameters obtained by common imaging modalities are considered in order to predict the risk of fracture, which is increased for large lytic lesions occurring in weight-bearing areas, and extending beyond the cortical bone. Some of these parameters have been considered by Mirels, who described a score [14] to predict the risk of fracture for long bone metastases. Patients reporting a Mirels' score ≥ 8 are considered at high risk and therefore, should be offered dedicated consolidative therapies.
Consolidative options differ according to the bone involved and to the typical physical stresses occurring on the target bone. In particular, it seems crucial to establish whether pure compressive forces occur or whether a combination of compressive and torsional/bending forces are involved.
In bones where pure compressive forces act (i.e. vertebral body, acetabulum, femoral condyles, proximal tibia, talus and calcaneus), percutaneous injection of poly-metyl-methacrylate (PMMA) allows effective bone consolidation, prevention of pathological fractures and effective pain management. PMMA is injected as a toothpaste material and

once deposited into the bone defect, it solidifies within 20-30 minutes. PMMA polymerization is an exothermic process with transient temperature raise. However, the cytotoxic effect of the polymerization is limited (if PMMA polymerization raises to 75°C the cytotoxic effect is limited to 3 mm around the cement [15]), even though it is sufficient to cause nociception nervous terminals destruction [16]. Moreover, if we consider that PMMA distribution inside the bone defect is unpredictable [17], one can easily figure out that PMMA does not allow any kind of local tumor control. Therefore, percutaneous cementoplasty should always be preceded by an ablative radical treatment if the goal of treatment is curative.

PMMA-mediated micro- and macro-fracture consolidation as well as nociception terminals destruction due to the exothermic polymerization make percutaneous cementoplasty a valid consolidative treatment in weight-bearing bones.

In bone districts where torsional/bending act along with compressive forces (i.e. pelvic ring, long bone diaphysis), percutaneous cementoplasty alone does not seem sufficient to achieve effective consolidation. Therefore, other forms of surgical or non-surgical consolidations (i.e. endo-medullary nailing, external fixation, screws) are proposed alone or in combination with PMMA injection.

- *Available evidence*

Several different studies proved that percutaneous PMMA injection into spinal lesions (i.e. vertebroplasty) is a safe and effective treatment providing rapid analgesia and structural reinforcement in patients affected by metastatic bone disease.

The European VErtebroplasty RESearch Team (E.VE.RES.T) prospectively enrolled 4547 patients affected by vertebral compressive fractures (VCFs) caused by several different pathologies (e.g. osteoporosis, trauma, metastases, etc.) in order to evaluate pain relief on 0-10 points VAS at baseline and then at 48-hour and 12-month follow-up [18]. A reduction of at least 2 points was considered a positive result. A sub-analysis of 644 patients presenting with VCFs caused by malignant bone disease showed a significant VAS score reduction at 48-hour follow-up as compared to pre-treatment (mean pre-treatment 8.3 ± 0.4 vs mean post-treatment 2.4 ± 0.4, $p < 0.001$). No significant changes of the mean 48-hour VAS score were noted at 12-month follow-up (mean VAS score 2.9 ± 0.5, $p > 0.05$). Retreatment for a subsequent fracture was needed in 5.5% of the patients.

The Cancer Patient Fracture Evaluation study prospectively enrolled and randomized patients with known neoplastic disease, moderate pain (≥ 4 in a 0-10 VAS) and Roland–Morris disability (RDQ) score > 10 to receive percutaneous kyphoplasty or conservative non-surgical management [19]. Kyphoplasty was performed in 65 patients and conservative treatment in 52 patients. Clinical follow-up was obtained at 1-, 3-, 6-, and 12-month. The primary end-point was RDQ assessment at 1-month. Secondary outcome was composite and included several different tests along with evaluation of the VAS and RDQ scores at 1-, 3-, 6-, and 12-month. Due to the high primary-disease related mortality, only 74 patients completed the 12-month follow-up. The primary outcome, was significantly improved by 8.4 points in the kyphoplasty group vs 0.1 points in the group of patients receiving conservative treatment ($P < 0.0001$). Such RDQ improvement for the kyphoplasty group was still evident at 6-month follow-up but not at 12-month. The VAS score was significantly better for the kyphoplasty group at 1-month but not at further follow-up. In the whole, all the tested outcomes favoured kyphoplasty over conservative treatment at all time points, but statistical significance vanished as time passed by probably due to the relative few patients remaining in the conservative treatment group. Two major procedure-related complications were reported in the kyphoplasty group (i.e. one intra-operative myocardial infarction and one new fracture in the adjacent-level of treatment 1 day following the procedure).

Several different series prospectively and retrospectively analysed the performance of percutaneous cementoplasty applied in "extra-spinal" bones [20-27].

In particular, the largest series available [20] enrolled 51 patients undergoing extra-spinal cementoplasty for painful bone metastases; in 7 patients cementoplasty was combined with RFA. Seventy lesions were treated (mean size 36 mm). Along follow-up ranging between 15 and 36 months, mean VAS score dropped from 9.1 to 2.1. Forty-seven patients (94%) suspended narcotic drugs. No complications were noted. Two patients with metastases in the femoral diaphysis reported a fracture 1 month after treatment. Therefore, authors concluded that cementoplasty is effective to obtain pain regression in painful extra-spinal bone metastases; however, bone consolidation is not obtained in the diaphysis of long weight-bearing bones.

Another large study [26] collecting the 10-years' experience of an oncologic tertiary centre in 51 consecutive patients affected by painful long-bone metastatic lesions, reported a secondary stress fracture rate of 9.1% (6 fractures out of 66 treated lesions; mean time to fracture of 3.2 months; range 0.5-11). All the lesions reporting a fracture had high pre-operative Mirels' score (mean 9); and, four fractures needed surgical interventions external fixation.

Cazzato et al [28] reviewed the outcomes and local evolution of pathological/insufficiency fractures and impeding fractures in cancer patients undergoing percutaneous image-guided screw fixation (PIGSF) at two different tertiary centres; 32 patients were enrolled and screws were deployed with or without cementoplasty. Clinical outcomes were assessed using a simple 4-point scale (1 = worse; 2 = stable; 3 = improved; 4 = significantly improved); and local evolution was assessed by common imaging modalities (i.e. CT). Thirty-six lesions were treated with 74 screws mainly deployed in the pelvis and femoral neck (58.2 %). In the whole, authors treated 47.2 % pathologic fractures, 13.9 % bone insufficiency fractures, and 38.9 % impending fractures. Cementoplasty was performed in 63.9 % of the cases; and, 87.1 % lesions were clinically improved at 1-month follow-up. Three major complications (i.e. early screw-impingement radiculopathy; accelerated coxarthrosis; late coxofemoral septic arthritis and one minor complication) were observed. Unfavourable local evolution at imaging occurred in 12.5 % cases (mean 8.7-month follow-up), including poor consolidation (one case) and screw loosening (two cases, at least 1 symptomatic). There were no cases of secondary fractures. Authors concluded that PIGSF was feasible for a wide range of oncologic patients, offering good short-term efficacy, acceptable complication rates, and rapid recovery. Unfavourable local evolution at imaging may be relatively frequent thus, requiring close clinical and radiological follow-up.

Robust evidence obtained from large, prospective multi-center series and from prospective randomized trials support the palliative application of percutaneous vertebroplasty in assuring rapid pain relief and long-lasting bone consolidation in patients with malignant spinal disease (SIGN 1++).

Less robust evidence obtained from prospective and retrospective case-series proved that percutaneous cementoplasty might be applied to obtain rapid pain relief in "extra-spinal" bone metastases (SIGN 2++). However, it has been figured out that in bone districts where forces other than purely compressive (e.g. femoral diaphysis) act, PMMA consolidation seems suboptimal thus, requiring other consolidative measures alone or in combination with PMMA.

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2. BIOMECHANICS AND PMMA CONSOLIDATION IN LONG BONES

2.1 Basic biomechanics

There are four basic modes of loading: compression, tension, bending and torsion. Accordingly, there are four different structures whose configuration can contrast each different mode of loading: columns carry compressive forces, ties tensile ones, beams bending ones and, shafts torsional ones.

Forces are defined normal or direct when they act perpendicularly to the plane of load; and, shear when they act parallel to it.

Normal forces change the shape and volume of a target structure; shear forces can only change its shape.

2.2. Bone structure

Bone is a composite material made of mineral salts (i.e. hydroxyapatite and calcium carbonate) reinforcing a collagenous matrix (i.e. collagen type 1). Mineral salts contribute stiffness (i.e. material resistance to change in shape) and hardness (i.e. material resistance to localized surface plastic deformation); on the other hand, collagen fibres contribute toughness (i.e. material ability to absorb energy up to fracture) and strength (i.e. load required to break a material).

Mineralized collagen fibres are organized in different layers of sheets, called laminae, and cylinders, called osteons, which must be all individually broken in order to have a complete fracture of the target bone. Therefore, such microscopic laminar structure prevents bone from progressing into complete fractures in normal conditions.

Collagen fibres are arranged and aligned longitudinally in long polymeric chains. Covalent bonds link molecules within a single chain; on the other hand, secondary bonds link the longitudinally aligned polymeric chains.

Macroscopically, the laminar structure constitutes cortical bone, which is dense and stiff. On the other hand, cancellous bone is less dense and more malleable.

Bone is a dynamic viscoelastic tissue, whose final configuration is the result of a dynamic equilibrium between osteoclasts and osteoblasts activity: the formers contribute mineral and protein reabsorption and the latters lay down new mineralized collagenous matrix. As results, bone can continuously adapt to the specific functional demand of each single subject; and, such adaptation is done in order to have the minimum-mass structure needed to sustain the applied load (Wolff's law).

2.3 Bone mechanical properties

The most important mechanical property of bone is stiffness, which allows resistance to deformation under load and the possibility to maintain body's upright posture.

Depending on the subjects' age, the viscoelastic biomechanical properties of bone are different. In children, bone is much less mineralized; and as a result, it is much less stiff and much more pliable than it happens in adults, in order to respond to low-energy injuries typical of the juvenile age. On the other hand, the densely mineralized bone of an adult is very stiff but brittle thus, resulting very resistant to compressive stresses. Such goal is reached thanks to the covalent bonds present in the longitudinal polymeric collagenous chains; therefore, a longitudinal applied load (e.g. upright posture) works against stiff and strong bonds; on the other hand, transverse applied loads work against weak secondary bonds. Therefore, bone structure allows much more stiffness to compression than to bending, torsion or shearing.

2.4 Bending stress, beam theory and long bone biomechanics

A beam is a structure much longer than larger capable to support bending stresses. When a bending force (acting perpendicularly to the long axis of the beam) is applied to a beam, such force is transferred by the beam itself to the adjacent supports. As a result, shear forces and bending moments are generated and subsequently transferred to supports. According to Newton's third law, also the supports exert a reaction force to the beam. Therefore, when combined, the applied and reaction forces are equal and opposite thus, allowing equilibrium to the beam.

At the same time, when the bending force is applied to a beam, it produces compressive stress on its side and tensile stress on the external side of the beam. In the middle of the beam, the "neutral axis" does not change its length since, neither compressive neither tensile stresses act on it. Compressive and tensile stresses increase progressively with the increasing distance from the neutral axis and are highest on the external surface of the beam.

The cross-sectional distribution of material in a beam is defined as "area moment of inertia"; and, the larger the "area moment of inertia", the greater the bending resistance of the material. Moreover, different cross-sectional shapes and areas provide different resistance to bending. In particular, structures are more resistant to bending when the cross-sectional material is distributed far away from the neutral axis, like it happens for hollow cylindrical structures. Bending stiffness of a hollow beam is related to the thickness of its wall and the outer diameter, with the latter playing a more important role compared to the former in conferring resistance to bending stresses. The main drawback of a hollow beam is that, if it is loaded beyond its strength, it fails more suddenly than a solid beam, as there is much less material for a fracture to propagate across.

Adult bone is a brittle material being much more resistant to compression rather than to bending or torsion. Therefore, bending and torsion generate some of the highest stresses on bones.

Long bone geometry consistent with a hollow cylinder, optimise resistance against bending and torsion without compromising strength in compression [1].

2.5 Experiences available with interventional long bone consolidation: Is PMMA suitable for long bones?

In the largest series available about extra-spinal cementoplasty (50 patients, 70 treated lesions) Anselmetti et al [2] highlighted the great performance of PMMA in managing pain generated by lytic bone metastases. The only two complications reported in the series were noted in two patients affected by metastases in the femoral diaphysis, who reported a secondary stress fracture 1 month after the treatment. Surgical fixation was needed to treat such fractures. Therefore, they concluded that lytic lesions of the long bone shaft might be treated with percutaneous cementoplasty to obtain pain regression; however, further surgery must be considered to reduce the risk of fracture during ambulation.

Cazzato et al [3] retrospectively reviewed the data concerning 51 patients who underwent percutaneous cementoplasty in patients meeting one or more of the following criteria: long bone metastasis or myeloma; high risk of fracture; unresponsiveness to previous analgesic treatment and/or to radiation therapy and/or to surgical treatment; life expectancy > 1 month. Patients were not eligible for surgical treatments since: surgery was considered too demanding either relative to the clinical/oncological status of the patient, either relative to surgeon's technical concerns; surgery would have delayed too much the beginning of chemotherapy.

Sixty-six lesions were treated in 51 patients. Local pain palliation at 1-month was significant in 47.0% and mild in 42.4% cases, respectively. In 10.6% cases, pain was unchanged, and it never worsened as compared to baseline. Pain improvement was more common for lesions of the upper limb (humerus and radius) rather than for those of the lower limb ($p < 0.05$).

Limb function at 1-month improved significantly in 42.2% and mildly in 29.7% cases, respectively. It remained unchanged in 25.0% cases, and worsened in 3.1%. Lesions sized ≤ 3 cm were more likely to result in better functional amelioration ($p < 0.05$).

One major complication involving cement leakage into the elbow joint space with subsequent permanent limitation of arm extension was reported. However, this loss of function did not require surgical extirpation of the leaked cement. As a whole, 6/66 (9.1%) lesions developed a secondary pathological fracture (4/6 requiring external surgical fixation) with a mean time interval of 3.2 months (range 0.5-11).

Authors concluded that cementoplasty is a safe and effective option with optimal rates of early pain relief and functional improvement. The procedure was complicated by secondary fracture in up to 9% cases; and, therefore, if fracture occurs following cementoplasty, only surgical external fixation remains an affordable surgical option.

Another limited but significant experience was reported by Deschamps et al [4], who applied percutaneous cementoplasty to consolidate lytic bone metastases in the proximal femur. Authors retrospectively analysed all consecutive patients who underwent cementoplasty for metastases of the proximal femur with a concomitant high risk for fracture ($N = 21$) in order to prevent the risk of fractures (all patients) and also to alleviate pain in 16 patients. The 1-year secondary fracture rate was 40.6% (seven fractures). The risk of fracture correlated with cortical involvement greater than 30 mm ($p = 0.0005$) and a history of a previous fracture of the lesser trochanter ($p = 0.0009$).

Authors concluded that percutaneous cementoplasty could be considered for patients with metastases of the proximal femur when cortical involvement is limited (less than 30 mm) and no history of a fracture of the lesser trochanter is present.

However, few years later the same group published a new series about patients with impending fractures of the proximal femur (Mirels' score ≥ 8) undergoing percutaneous osteosynthesis in addition to cementoplasty [5]. They performed the combined technique in 12 patients not candidates for standard surgical stabilization. All patients stood-up and walked the second day after the procedure. No fractures occurred after a median follow-up of 145 (range, 12-608) days, and for symptomatic patients (n = 8), VAS decreased from 6.5/10 before treatment to 1/10 1 month after.

Therefore, authors concluded that the combination of screws and cementoplasty is a safe and effective consolidative technique for the treatment of impending fractures of the proximal femur in cancer patients who are not candidates for surgical stabilization.

Lin et al [5] compared the efficacy of percutaneous long bone cementoplasty (PLBC) with and without embedding a cement-filled catheter in the medullary canal (ECFC) for painful long bone metastases presenting with an impending fracture.

Authors retrospectively analysed a population of 36 consecutive patients undergoing PLBC plus ECFC (n =17, group A) or PLBC alone (n = 19, group B). Overall pain relief was significantly higher in group A than in group B (88.2 % vs. 57.9 %, $p < 0.05$). The average visual analogue scale and Karnofsky performance scale changes in group A were significantly higher than those reported in group B 1-, 3- and 6-months post-operatively ($p < 0.05$). In the end, the rate of fractures in group A was significantly lower than that in group B ($p < 0.05$). Authors concluded that combined PLBC and ECFC is a safe and effective procedure for long bone metastases determining an impending fracture.

Cazzato et al [6] published a systematic review about percutaneous long bone cementoplasty for palliation of malignant lesions of the limbs. They included published papers between 1994 and 2014, basing the literature search on "percutaneous cementoplasty" as keywords. In the end, they included all studies matching the following criteria: (a) prospective/retrospective cohort studies applying percutaneous cementoplasty to treat primary or secondary bone tumours; (b) cohort of at least 10 patients; (c) at least 1 patient in the cohort undergoing percutaneous cementoplasty of the humerus, radius, ulna, femur, tibia or fibula; (d) papers published in english; (e) results not published twice by the same author.

Thirteen full manuscripts (4 prospective, 9 retrospective) matched inclusion criteria and entered the final analysis. In the whole, a population of 382 patients was analysed and 196 patients were treated with percutaneous cementoplasty, accounting for 223 lesions (mean size 45mm). Lesion location was: femur (64%), humerus (17%), tibia (10%), fibula (3%), and radius (1%); 5% lesions were in unspecified locations. Four papers gave further details about tumour location inside the affected bone: 50% lesions were epiphyseal, 44% metaphyseal, and 6% diaphyseal. Percutaneous stabilization was performed in three papers (17% procedures) by applying: a) cannulated screws inserted percutaneously in the proximal femur; b) endo-medullary flexible nails to stabilise bone lesions of the lower limbs; c) a biliary cement-filled catheter inside the endo-medullary cavity. All these techniques of stabilization were always combined to cementoplasty. The correlation test between percutaneous stabilization and absence of secondary fractures did not provide any statistical significance ($p = 0.08$), probably, because the subgroup of patients receiving some kind of percutaneous stabilization in addition to cementoplasty was very small (32 patients). Twelve papers studied the incidence of "secondary fractures", which occurred in 16 cases (8%). All these fractures occurred in the group of patients receiving cementoplasty alone, without one of the three options of percutaneous stabilization. In facts, despite the heterogeneous technique of percutaneous stabilization applied and the low proportion of patients receiving it in addition to cementoplasty, no secondary fractures occurred in this sub-population at a mean 9.9 months follow-up.

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3. SPECIAL SECTION: LONG BONE CEMENTOPLASTY TESTED ON A CADAVERIC MODEL

3.1 Materials and Methods

Institutional review board approval was obtained for this cadaveric study.

3.1.1. Bone specimens

All anatomical specimens used for this study were from human cadaver donations to the Anatomy Department of the "Hopitaux Universitaires de Strasbourg". Bone specimens consisted of 10 pairs of embalmed cadaver tibiae, injected with formalin and alcohol solution through the femoral artery and kept in 20% alcoholic solution before being used in the study. In total, all ten pairs of excised tibiae were tested. Tibiae were harvested in compliance with institutional safety regulations.

The mean age of cadavers was 75 years (range 67 - 93 years) and the cause of death was unknown. The mean patient height was 1.67 m (range 1.52 - 1.78). None of the cadavers had any known oncologic disease, prior surgery or anatomic correction of the legs that could preclude the current study tests and analysis.

Each tibia was measured along its long axis from the proximal to the distal epiphysis and then cut in the middle; therefore, from each cadaver, 4 different specimens (proximal right and left hemi-tibia and distal right and left hemi-tibia) were obtained. Among the 40 bone units, 30 were randomly selected and equally assigned to receive:

1) No endo-medullary (EM) reinforcement *(Group 1)*;
2) Osteoplasty *(Group 2):* EM injection of polymethyl-methacrylate (PMMA, Osteopal V, Heraeus Medical GmbH, Wehrheim, Germany) into the diaphyseal shaft under continuous fluoroscopic guidance until complete filling;
3) Kirshener-augmented osteoplasty *(Group 3):* EM insertion of 3 kirshner wires (diameter 2 mm) with a triangular configuration into the diaphyseal shaft, coupled to PMMA injection under continuous fluoroscopic guidance in the centre of the triangle until complete filling.

The three groups are presented in **Fig. 1.** The remaining 10 bone specimens were used for pre-clinical technical feasibility assessment. In particular, six specimens were used to test the technique from group 2 and group 3, and the other 4 were used to test a recently reported interventional technique for EM reinforcement [18,19] being consistent with an EM PMMA-filled biliary catheter. Such catheter is then intended to work like an EM nailing in order to increase the reinforcing properties of PMMA injected into the dyaphyseal shaft. Although conceptually not much different from simple osteoplasty, we were keen in testing such novel technique since interventional radiologists are quite familiar with PMMA and catheters [23]. Unfortunately, from a technical point of view, in our limited experience, the biliary-catheter technique was not consistently reproduced as efficient and homogeneous PMMA distribution inside the biliary drainage was not obtained with 5 different catheters (ranging between 8Fr and 14Fr, 4 inserted into a dyaphyseal shaft and one outside a bone unit) injected manually by means of 3 ml syringes at controlled room temperature (22°C; **Fig. 2**). Hence a subgroup of biliary PMMA-filled catheter was not considered.

Once assigned to one of the 3 groups and before being injected (group 2 and 3), all the 30 bone specimens included underwent conventional CT scan (90 mAs; 120 kV) in order to assess cortical bone density. The bone density was measured in 3 different points at the epiphyseal, metaphyseal and diaphyseal cortices respectively, by means of 3 different regions of interest (1 mm^2). The mean value obtained by these three measures represented the cortical density assigned to each specimen.

3.1.2. Biomechanical tests

All specimens were tested on a dedicated servohydraulic machine (INSTRON 8500 plus, INSTRON corporation, High Wycombe, Buckinghamshire, United Kingdom) in three-point bending. Specimens were positioned horizontally by two fixed supports, with their lateral aspect facing inferiorly and centrally loaded. The vertical load onto the cortical bone was applied through a metal triangle attached to the loading cell (**Fig. 3**). An application of a 10 N pre-load was performed, following which a steady vertical load was carried on all specimens using the machine actuator, which created inferior translation at the contact point by 50 mm/sec. The loading was carried on till cortical bone fractured. In function of time, the strain applied to the tibia was recorded by the INSTRON load cell and transferred to an Excel sheet (version 8 for Windows; Microsoft Corporation, Redmond, WA); strain-stress curves were created for each construct with data acquisition frequency of 2500 points per second. The obtained strain/stress curves allowed automated determination of fracture load and Young's modulus corresponding to the maximal deformation under elastic conditions.

3.1.3. Data collection and analysis

For each specimen the following parameters were collected: longitudinal length, cortical bone density, quantity of injected PMMA, fracture load and Young's modulus.

Following biomechanical testing, each specimen underwent X-ray in two perpendicular projections in order to assess fracture occurrence and its morphology both to bone and eventually to EM material.

Bone fractures were classified according to a modified version of Long Bones Fractures classification of the Müller AO Trauma Foundation [20]; additionally, a 0 score was added to the traditional classification to represent unilateral cortical fractures not extending to the opposite cortex (**Fig. 4**). Fracture evaluation both to bone specimens and to the EM material, was performed in consensus by two board-certified radiologists with 2- and 5-years of experience, respectively.

Descriptive statistics were used to present results. Two-sample Wilcoxon rank-sum test was used to compare fracture load and Young's modulus between different groups; Spearman (rho) test was used to correlate quantitative variables; $p < 0.05$ was considered statistically significant.

3.2. Results

Results are presented per group. Features of different bone specimens recruited in each group by randomisation, median specimens length and cortical density are summarized in **Table 1**.

Mean and median fracture load and mean and median Young's modulus are summarized in **Table 2** for individual groups**.** The median quantity of PMMA injected into the specimens of groups 2 and 3 was 18 ml (p25-p50; 15-21) and 19 ml (p25-p50; 17-21), respectively. In terms of fracture load, there was no significant difference between group 1 and 2 ($z = -0.793$; $p = 0.4295$), group 1 and 3 ($z = -0.944$; $p = 0.3472$), and group 2 and 3 ($z = -0.454$; $p = 0.6501$). Young's modulus also did not differ significantly between group 1 and 2 ($z = 0.121$; $p = 0.9044$), group 1 and 3 ($z = 0.338$; $p = 0.7278$), and group 2 and 3 ($z = 0.148$; $p = 0.8807$).

The most common types of bone fracture recorded in the series were A0 (14/30, 46.6%) and A2 (8/30, 26.6%) (**Table 3**). Fractures to the EM material occurred in 4 cases (4/40, 10%): one fracture occurred to the PMMA injected in a bone specimen of group 2, and 3 fractures occurred to the PMMA injected in 3 specimens of group

3; no fractures were recorded to the metal EM material applied in group 3.

3.3.1 Discussion

In the last few years, interventional radiologists' interest has progressively grown in the field of long bone metastases treatment. Several different techniques have been proposed [8–14] through small limited mono-centric studies; however, all the proposed techniques substantially lacked preclinical biomechanical analysis.

Osteoplasty represented the first adopted technique [11,15] due to interventional radiologists' familiarity with PMMA injection in non-vertebral bones [16,21]. As expected, PMMA confirmed its optimal analgesic properties [11]; however, due to its physical properties conferring greater resistance to compression rather than to torsion or bending (compressive strength 93.0 MPa, bending strength 64.2 MPa [22]), PMMA appeared unsuitable for long bone diaphysis consolidation. This aspect was clearly reflected in clinical studies reporting a secondary rate of fractures ranging between 8 and 9.1% following long bone PMMA-mediated reinforcement [11,15]. In accordance with these observations, the present study confirmed the PMMA unsuitability to confer a significant resistance to diaphyses undergoing bending stresses as compared to native non-PMMA injected diaphyses. At the same time, the Young's modulus also reflected that bone elasticity did not differ between the tested groups. Based on such observations, surgical EM nailing should be still considered the gold standard for the treatment of pathologic/impending fractures of the diaphyseal shaft [6]. Surgical nailing acts like an internal splint with load-sharing features; and, it is usually provided of proximal and distal inter-locking systems thus, preventing telescoping and providing resistance to bending and torsional stresses [23,24].

Alternatives to classical EM nailing are flexible EM nailing and bundle nailing (**Fig. 5**); both techniques are commonly performed percutaneously thus, potentially being feasible by interventional radiologists.

Flexible EM nailing works like a spring through a 3-point fixation system; in facts, two pre-curved pins are inserted inside the medullary cavity in order to fix proximally and distally so that the apex of the curvature is at the level of the fracture. As a consequence, a dynamic equilibrium is obtained between the tensioned pins and bone, and intact surrounding muscle/soft tissue play a significant role to keep bone fragments aligned. Due to the elastic properties of flexible nailing, its application has been largely adopted for the treatment of traumatic long bone fractures in children [25]. On the other hand, very little has been published about this technique in cancer patients. In this perspective, Kim et al [13] applied EM flexible nails coupled to PMMA injection in 15 consecutive patients affected by long bone metastases of the lower limbs. At different time intervals, they reported a significant improvement both of pain and ambulation ability; moreover, in 9/15 patients receiving PET-CT evaluation before and after percutaneous consolidation, the target lesion showed a significant reduction both of SUV max and SUV mean after the intervention. The same group reported about another similar experience consisting with EM flexible nail coupled to PMMA injection to fix humeral metastases [14]; no fixation failure was reported.

Bundle nailing is another alternative to EM nailing and is consistent with multiple pins insertion inside the medullary cavity until complete filling in order to provide a tight compression between nails and bone [20].

Advantages of flexible and bundle nailing are related to their technical easiness, minimal invasiveness and resistance to bending; however, telescoping and resistance to torsional stresses are not granted as with inter-locking nailing. As a consequence, interlocking nailing provided better results in terms of fracture reduction and stability when tested in large series of traumatic fractures [27].

Group 3 model tested in the present series should not be considered similar to flexible or bundle nailing since it lacked a 3-point fixation system and EM pins filling. In facts, as demonstrated in the study, the triangular parallel k-wires configuration designed for group 3 did not offer any significant resistance to bending as compared to group 1 or 2.

The most common pattern of fracture registred in our series was type A0, which was a simple linear cortical fracture not extending to the full circumference of the cortex; the second most common type of fracture was A2 which is a simple oblique fracture. In addition there were 4 pure transverse (A3) and 2 multi-fragmentary wedge-shaped fractures (B3). All these morphologies are strictly in accordance with the applied bending stress. On the contrary, a note is made of spiral fracture pattern in 2 specimens (A1) indicating a torsional component at the time of the application of the beinding stress.

The fracture to the EM material was noted in 4 cases and all these fractures were a break through the PMMA, which indicates the brittle nature of PMMA not withstanding the bending/torsional stress. On the other hand, no fractures of the K-wires were noted, which can be attributed to their elastic attitude.

Limitations of the present study include the low number of bone specimens available due to the limited number of cadavers available. As a consequence, only analysis of the bending stress was performed and torsional stress which also play a key-role in dyaphyseal biomechanics was not tested. The low number of recruited specimens also limited studying other percutaneous minimally invasive techniques such as flexible or bundle nailing; both of them are well-known in traumatic orthopedic literature and they only need further clinical testing in cancer patients.

3.4 Conclusion

Due to its physical and biomechanic properties, PMMA alone does not provide any significant resistance to bending stress as compared to native diaphyses; therefore, it should not be proposed to cancer patients with good life-expecancy and who are still active. Accordingly, surgical EM nailing still remains the gold-standard for reinforcement of long bone dyaphises and therefore, when clinically feasibile it should be proposed as a first-line treatment. In case of clinical unsuitability to surgical EM nailing, minimally invasive techniques (i.e. flexible or bundle nailing) may be considered by interventional radiologists in cancer patients. This latter option is desirable since both techquines are technically affordable for interventional radiologists and futher experience in cancer patients is required.

Table 1. Specimen's features

	Number of Inferior Specimens	**Number of Superior Specimens**	**Number of Right Specimens**	**Number of Left Specimens**	**Median Specimen Length (cm) (p25-p75)**	**Median Specimen density (HU) (p25-p75)**
Group 1	8	2	6	4	18.375 (17.9- 19.25)	1621 (1571- 1652)
Group 2	4	6	6	4	18.375 (17.6- 19.25)	1600 (1550- 1613)
Group 3	5	5	3	7	18.325 (18- 19.25)	1606.5 (1550- 1632)

Table 2. Fracture loads and Young's modules

	Fracture Load (N)		**Young's Module (N/m^2)**	
	Mean (SD)	**Median (p25-p75)**	**Mean (SD)**	**Median (p25-p75)**
Group 1	1077.6 (370.16)	1076 (807-1341)	397.15 (140.07)	361.385 (300.65 - 514.07)
Group 2	1221.5 (338.12)	1166 (1091-1391)	444.53 (153.48)	497.88 (309.77- 556.35)
Group 3	1230 (292.58)	1280.5 (1119-1448)	430.73 (140.14)	392.23 (344.59- 547.15)

Table 3. Type of fractures according to a modified version of the Long Bones Fractures of the Müller AO Trauma Foundation classification [20]

	A0	**A1**	**A2**	**A3**	**B0**	**B1**	**B2**	**B3**	**C0**	**C1**	**C2**	**C3**
Group 1	6	2	0	1	0	0	0	1	0	0	0	0
Group 2	5	0	4	1	0	0	0	0	0	0	0	0
Group 3	3	0	4	2	0	0	0	1	0	0	0	0
Total	14	2	8	4	0	0	0	2	0	0	0	0

Fig. 1. Fluoroscopic image reporting one bone sample from each group (from left to right: group 1, group 2 and group 3, respectively).

Fig 2. Two 8Fr (**A, B**) and one 14Fr (**C**) biliary catheters were previously inserted inside the medullary space of 3 different bone units through a 10 G vertebroplasty trocar before being injected with PMMA. Another 8Fr catheter was injected with PMMA outside the bone (**D**). In all cases, PMMA did not spread distally inside the catheter, and solidified few minutes after injection in the proximal part of the catethers (arrows); moreover, in one case, the catheter broke at its proximal part due to the hard consistency of PMMA not spreading distally (**D**). In all cases PMMA was injected manually by means of 3 ml syringes, at controlled room temperature (22°C).

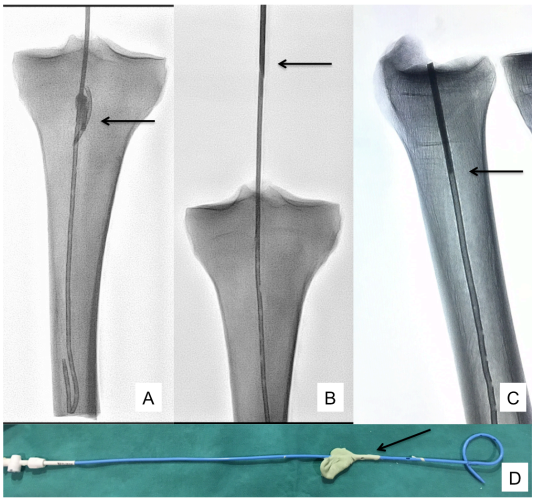


Fig 3. "Bending stress" test performed by means of the servohydraulic machine.

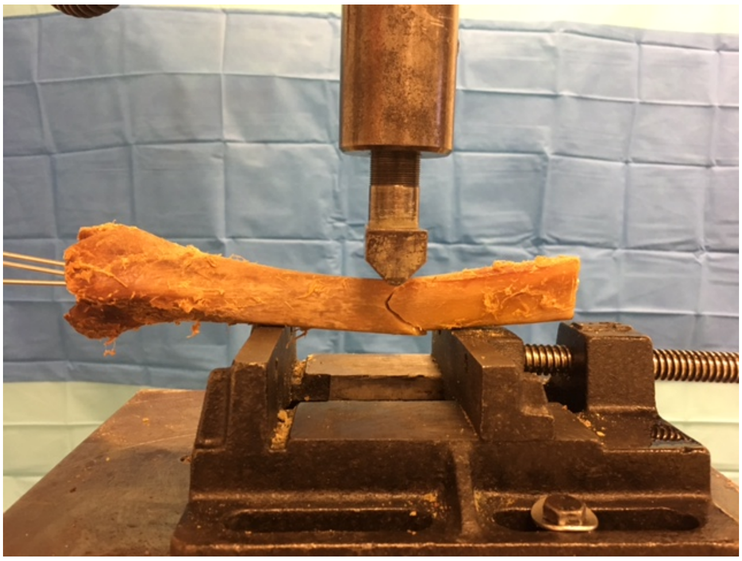


Fig 4. Schematic representation of the type "0" fracture.

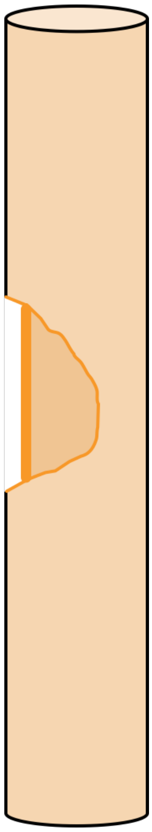
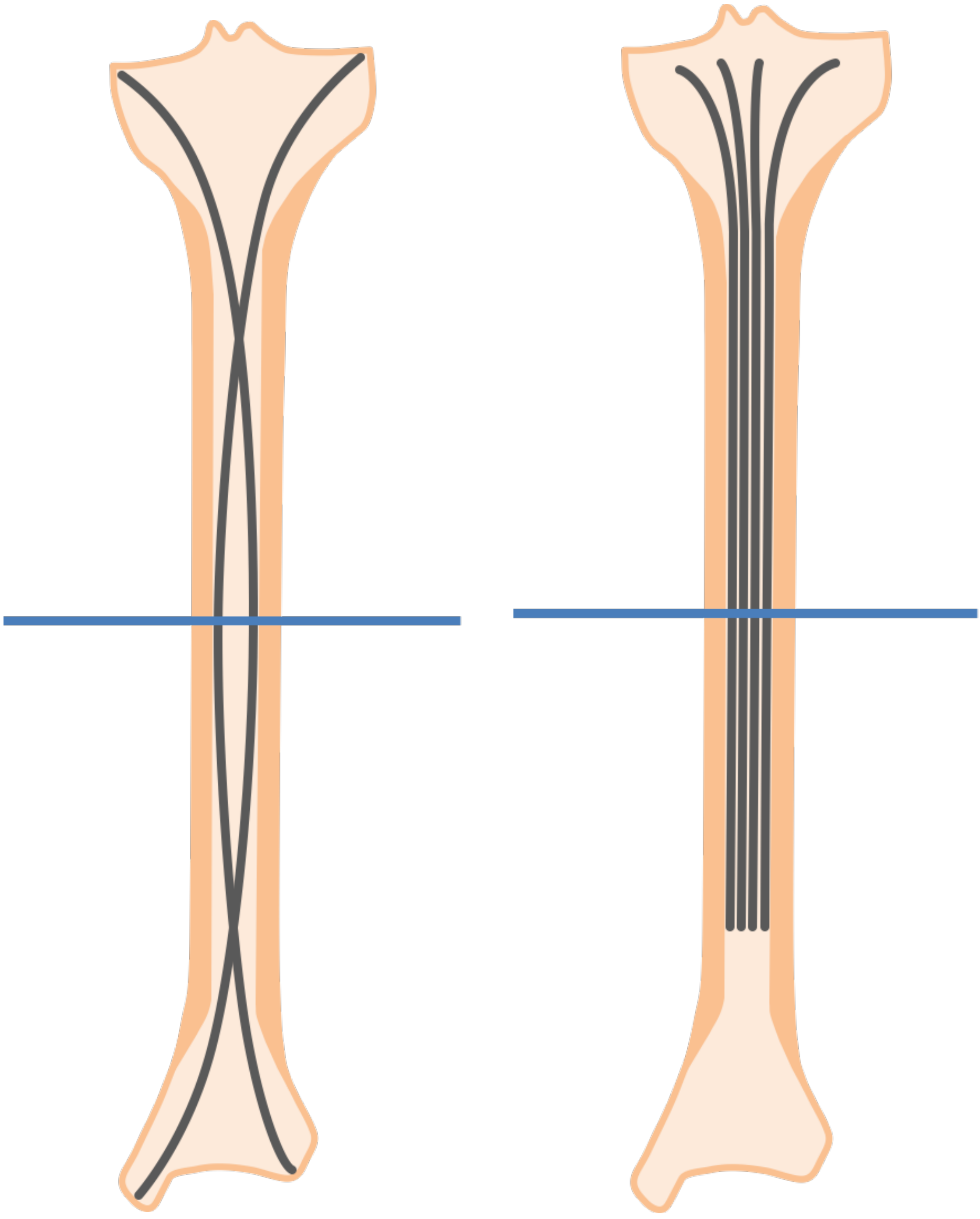


Fig. 5. Schematic representation of flexible (left) and bundle nailing techniques (right). Blue lines represent the level of fracture.



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5. APPENDIX: LIST OF PUBLISHED PAPERS DURING THE PhD PERIOD:

(+ Papers of interest in the field of osteo-oncology)

+ 1: Tsoumakidou G, Too CW, Koch G, Caudrelier J, Cazzato RL, Garnon J, Gangi A.
CIRSE Guidelines on Percutaneous Vertebral Augmentation.
Cardiovasc Intervent Radiol. 2017 Jan 19. doi: 10.1007/s00270-017-1574-8.
PMID: 28105496

+ 2: Percutaneous image-guided screws meditated osteosynthesis of Impeding and pathological/insufficiency fractures of the femoral neck in non-surgical cancer patients.
Cazzato RL, Garnon J, Tsoumakidou G, Koch G, Palussière J, Gangi A, Buy X
Eur J Radiol 2017, in press

3: Edalat F, Cazzato RL, Garnon J, Tsoumakidou G, Avérous G, Caudrelier J, Koch G, Gangi A.
Percutaneous Biopsy of Retrobulbar Masses: Anatomical Considerations and MRI Guidance.
Cardiovasc Intervent Radiol. 2016 Dec 8.
PMID: 27933376

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