

Osteointegração e sucesso em revisão acetabular de artroplastia total de quadril com enxerto estrutural homólogo: seguimento médio de 9,6 anos

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Abstract

Keywords

- ► arthroplasty, replacement, hip
- ► grafting bone
- cross-sectional studies
- ► osseointegration
- ► transplantation, homologous, reoperation.
- ► osteointegration

Objective To evaluate the clinical and radiographic results and survival of the acetabular revision surgery of total hip arthroplasty with cemented implant without the use of reinforcement ring, associated with structural homologous bone grafting. Methods A total of 40 patients (44 hips) operated from 1995 to 2015 were retrospectively analyzed. Radiographs were evaluated according to the classification of the acetabular bone defect, graft shape, and the presence of osseointegration. Cases were considered as failures when the migration of the implant was > 5 mm in any direction, and/or the progression of radiolucency lines around the acetabular component were > 2 mm. We verified the association of radiographic findings with cases of failure using statistical tests and analyzed survival using the Kaplan-Meier curve. Results Of the 44 hips, 45.5% of the acetabular defects were Paprosky type 3A and 50% were 3B. In 65% of the hips, the graft configuration was classified as Prieto type 1 and in 31% as type 2. No radiographic evidence of osseointegration was observed in

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13.6% of the cases. We observed 9 (20.5%) reconstruction failures. A correlation was observed between reconstruction failure and the absence of radiographic signs of graft osseointegration.

Conclusion We observed good clinic and radiographic results, with survival of 79.54% in a mean follow-up of 9.65 years. Also, there was an association between absence of radiographic signs of osseointegration of the structural graft and failure in this series of patients with large bone defects. The failures did not correlate with the severity of the acetabular bone defect, thickness, or graft configuration.

Resumo

Objetivo Avaliar os resultados clínicos, radiográficos e a sobrevida da cirurgia de revisão acetabular de artroplastia total de quadril com implante cimentado sem uso de anel de reforço, associado à enxertia óssea homóloga estrutural.

Métodos Um total de 40 pacientes (44 quadris) operados de 1995 a 2015 foram analisados retrospectivamente. As radiografias foram avaliadas de acordo com a classificação do defeito ósseo acetabular, o formato do enxerto e à presença de osteointegração. Foram considerados casos de insucesso a migração do implante > 5 mm em qualquer direção e/ou a progressão de linhas de radioluscência em torno do componente acetabular > 2mm. Verificamos a associação dos achados radiográficos com os casos de falha utilizando testes estatísticos e analisamos a sobrevida utilizando a curva de Kaplan-Meier.

Resultados Dos 44 quadris, 45,5% dos defeitos acetabulares eram Paprosky tipo 3A e 50%, 3B. Em 65% dos quadris, a configuração do enxerto foi classificada como tipo 1 de Prieto e em 31% como tipo 2. Não foi observada evidência radiográfica de osteointegração em 13,6% dos casos. Observamos 9 (20,5%) falhas de reconstrução. Foi observada correlação entre falha da reconstrução com a ausência de sinais radiográficos de osteointegração do enxerto.

Conclusão Observamos bons resultados clínicos e radiográficos, com sobrevida de 79,54% em seguimento médio de 9,65 anos. Também houve associação entre ausência de sinais radiográficos de osteointegração do enxerto estrutural e falha nesta série de pacientes com grandes defeitos ósseos. As falhas não se correlacionaram com a severidade do defeito ósseo acetabular, espessura ou configuração do enxerto.

Palavras-chave

- artroplastia de quadril
- ► enxerto ósseo
- ► estudos transversais
- ▶ osteointegração
- transplante homólogo
- ► reoperação

Introduction

Acetabular reconstruction surgery during total hip arthroplasty revision (THAR) is a complex procedure. Loosening of the implant after arthroplasty is one of the most frequent complications in the long term, leading to bone loss. The main objectives of acetabular reconstruction surgery are to obtain implant stability by restoring the hip anatomy with positioning of the component as close as possible to the center of joint rotation. 2

There are several forms of treatment of large acetabular bone defects in THAR: placement of implant with high hip center of rotation (High Hip Center), use of large diameter implants (Jumbo cup), use of structural homologous bone graft (with or without reinforcement ring), impaction of fragmented homologous bone graft (with or without reinforcement ring), in addition to the use of enlargements in trabecular metal. However, the most appropriate treatment remains undefined. 4,5

Our service started the use of homologous graft in THAR in the 1980s, with the subsequent publication of the results. ^{6–8} The analysis of our cases and the result of the literature allows the verification of homologous bone graft consolidation with possible osseointegration in most cases, allowing a stable reconstruction. ^{2,5} The use of bone graft makes it possible to restore the center of hip rotation, obtain implant stability, restore the acetabular integrity and bone stock, facilitating future revisions. ⁹ With the stability of the graft in reconstruction, it is possible to provide conditions for revascularization and osseointegration to the host bone. ⁹ The disadvantages that can be found with this technique are the potential resorption of the graft and the nonunion to the host bone. ^{10,11}

The aim of the present study is to evaluate the clinical and radiographic results and survival of acetabular reconstruction surgery with cemented implant without the use of reinforcement ring, associated with structural homologous bone grafting.

Materials and Methods

Between January 1995 and August 2015, 318 patients were submitted to THAR by 2 surgeons from the same medical team (Roos B. D. e Roos M. V.). Of these, 71 were submitted to THAR with the use of cemented acetabular implant without reinforcement ring associated with structural homologous

bone grafting. Thirty-one patients were excluded due to loss of follow-up, follow-up < 24 months, or for presenting incomplete medical records or exams. Forty patients were analyzed (44 hips) in a retrospective study (>Table 1).

The decision to use the technique evaluated in the present study was the preoperative radiographic finding of segmental or combined acetabular bone defects, in addition to large

Table 1 Clinical and demographic characteristics of cases (operated hips)

	Preoperative				Immediate postoperative		Late postoperative period	
#	Gender	Operated side	Age (Years)	ATK type	Date of surgery	Type of revision	Last follow-up (years + months)	Failure
1	Female	Left	40	Cemented	31/01/2007	Cemented	11y + 11m	No
2	Female	Right	46	Hybrid	12/05/2003	Cemented	8y + 4m	No
3	Female	Right	42	Girdlestone	13/11/2002	Cemented	14y + 11m	No
4	Male	Right	43	Cemented	21/02/2003	Cemented	9y + 1m	No
5	Female	Left	77	Cemented	16/07/2001	Cemented	4y + 2m	No
6	Female	Right	47	Not cemented	08/11/2006	Cemented	10y + 10m	No
7	Male	Right	67	Cemented	05/08/2002	Cemented	14y + 6m	No
8	Female	Right	72	Not cemented	17/09/2003	Reverse hybrid	11y + 10m	Yes
9a	Female	Right	64	Spacer	19/09/2005	Cemented	7y + 6m	Yes
10a	Female	Right	72	Cemented	13/05/2013	Cemented	7y + 10m	Yes
11	Female	Right	76	Partial	04/02/1997	Cemented	8y	No
12	Female	Left	57	Not cemented	20/11/2000	Cemented	15y + 4m	No
13	Male	Right	67	Cemented	02/08/2004	Cemented	6y + 1m	No
14	Female	Right	71	Cemented	07/11/2005	Cemented	4y + 9m	No
15b	Male	Right	42	Cemented	17/03/1998	Cemented	16y + 10m	No
16b	Male	Left	51	Cemented	14/05/2007	Cemented	7y + 8m	No
17	Male	Right	69	Not cemented	10/05/2001	Cemented	4y + 4m	No
18	Female	Right	78	Cemented	31/01/1995	Cemented	18y + 9m	No
19	Male	Right	72	Cemented	17/01/2008	Cemented	10y + 11m	Yes
20	Female	Right	43	Not cemented	24/06/2003	Cemented	14y + 2m	No
21	Male	Left	47	Cemented	19/11/1996	Cemented	16y + 7m	No
22	Female	Left	57	Not cemented	13/09/2000	Cemented	14y + 1m	Yes
23	Male	Left	59	Cemented	13/04/1999	Cemented	8y + 10m	No
24	Female	Right	72	Cemented	22/11/2006	Cemented	7y + 7m	No
25	Female	Left	65	Not cemented	06/09/2004	Cemented	4y + 0m	No
26	Female	Left	38	Not cemented	14/03/2003	Cemented	15y + 0m	No
27	Female	Left	62	Not cemented	19/05/2005	Cemented	13y + 8m	No
28c	Female	Right	38	Cemented	27/10/2005	Cemented	2y + 1m	Yes
29c	Female	Right	45	Cemented	30/07/2012	Cemented	7y + 2m	Yes
30	Male	Right	77	Cemented	25/10/2002	Cemented	6y + 6m	No
31	Female	Right	73	Not cemented	05/12/2007	Cemented	10y + 6m	No
32	Female	Left	61	Not cemented	21/12/1998	Cemented	12y + 3m	No
33	Female	Left	66	Cemented	25/10/2005	Cemented	13y + 5m	No
34	Female	Left	56	Not cemented	13/10/2004	Cemented	12y + 9m	No
35	Female	Left	41	Not cemented	03/07/2000	Cemented	16y + 3m	No

(Continued)

Table 1	(Continued)
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	Preoperative				Immediate postoperative		Late postoperative period	
#	Gender	Operated side	Age (Years)	ATK type	Date of surgery	Type of revision	Last follow-up (years + months)	Failure
36	Female	Right	70	Cemented	19/06/2007	Cemented	12y + 5m	No
37d	Male	Left	56	Cemented	27/09/1997	Cemented	6y + 10m	Yes
38d	Male	Left	63	Cemented	27/08/2004	Cemented	15y + 9m	No
39	Female	Right	70	Not cemented	10/08/2015	Reverse hybrid	3y + 2m	No
40	Female	Right	46	Not cemented	15/07/2015	Reverse hybrid	4y + 0m	No
41	Female	Right	63	Cemented	21/07/2015	Reverse hybrid	3a + 1m	Yes
42	Female	Right	64	Cemented	19/05/2015	Reverse hybrid	2a + 1m	No
43	Male	Right	69	Cemented	12/02/2015	Reverse hybrid	2a + 1m	No
44	Male	Left	59	Girdlestone	01/10/2014	Reverse hybrid	2a + 0m	No

Abbreviations: m, months; y, years.

Letters a, b and c indicate the same patient, but different surgery.

cavitary defects, with or without pelvic discontinuity (D'Antonio Classification¹²). The study was initiated after approval by the Ethics Committee of our institution.

Clinical Evaluation

Late pre- and postoperative clinical evaluation was performed in all patients using the Harris Hip Score (HHS) hip evaluation score.¹³

Radiographic Evaluation

Standardized radiographs of the pelvis were performed preoperatively, in the immediate postoperative period, and in the follow-up exams at 6 weeks, 3 months, 6 months, and, afterwards, annually.

The classification of the acetabular bone defect was preoperatively evaluated using the Paprosky¹⁴ and D'Antonio methods,¹² in addition to the size of the defect in millimeters.⁶

On immediate postoperative radiography, the percentage of coverage of the acetabular component by the structural graft and the measurement in millimeters of the largest craniocaudal thickness of the graft were evaluated. To describe the configuration of the structural graft in the acetabulum, we used the description published by Prieto et al., which defined it in three types: Type 1, buttress configuration or "flying buttress"; Type 2, dome support; and, Type 3, on base or "footing".

On later postoperative radiography, osseointegration of the graft was classified as described in another publication, which became known as the "Coon criterion". Type 1 was defined as total continuity of the bone trabeculate at the interface between the host bone and the graft (total osseointegration); Type 2, as partial continuity of the bone trabeculate at the interface between the host bone and the graft (partial osseointegration); Type 3, as absence of continuity of the bone trabeculate at the interface between the host bone and the graft (absence of osseointegration); and Type 4 as impossibility of visualization of the graft due to the presence

of prosthetic components (screens, reinforcement rings, etc.).

In serial radiographs, the presence of progressive radiolucent lines around the acetabular component, and signs of graft resorption and osteolysis were evaluated, according to the acetabular zones determined by DeLee et al.¹⁶

The migration of the acetabular component was measured in radiographs obtained in the immediate postoperative period compared to the later one, through parameters defined by Knight et al., ¹⁷ having as reference points the teardrop of both hips, the Köhler line, and the hip rotation center.

The reconstruction was considered a failure when there was loosening of the implant with migration > 5 mm in any direction, and/or the progression of radiolucent lines around the acetabular component > 2 mm wide. The cases of failure were compared with the others (success) seeking correlation with the classification of the bone defect according to Paprosky et al. ¹⁴ and D'Antonio et al., ¹² the size of the bone defect in millimeters, ⁶ the largest thickness of the graft in millimeters, the percentage of implant coverage by the graft, osseointegration of the graft, ¹⁵ the presence of graft resorption and osteolysis, in addition to its configuration. ¹⁸

To avoid inter- and intra-observer errors, the measurements were performed by one team member and reviewed by another. In case there was disagreement, a new evaluation was performed by a third member of the team, and then a consensus was reached.

Surgical Technique

We used the modified Hardinge anterolateral surgical approach in all cases. Initially, the acetabular component is removed; later, debris and fibrous tissue are cleaned from the cavity, using curettes and acetabular cutters, to reach a surface that is cruent and able to receive the graft. Then, the removal of the femoral stem is performed when necessary.

The graft is prepared and washed with saline, block graft was used on the acetabular ceiling associated or not with a

chopped graft. After cleaning the acetabulum, a bed is prepared with impacted chopped graft at the site that will receive the bone block, so that there are no "dead zones" that allow the formation of fibrous tissue or cysts, hindering the consolidation and possible integration of the block.

The fixation of the structural graft in the host bone is through 3.5 mm spongy screws with partial thread, at a 45° angle and in variable number according to the size and number of bone blocks used. After fixing the graft, the cavity is milled until it reaches the ideal size. After complementary filling of the existing defects, the acetabular component is placed, cemented or not, and at least one anchorage is performed, made superiorly with a 10 mm drill, necessarily reaching the host bone, and another made in the ischium through the host bone, impacted graft, or bone block (depending on the size of the existing cavity). We used an iodopovidone solution with saline solution throughout the transoperative period.

Postoperative Management

Mechanical thromboembolic prophylaxis was used in the immediate postoperative period, prophylactic oral anticoagulation for 30 days and antibiotic prophylaxis with vancomycin and ceftriaxone. In addition, one gram of ceftazidime is added to each dose of bone cement used. A radiographic evaluation is performed 6 weeks after the surgical procedure, from that moment on, full support with a crutch is allowed as an accessory element of balance.

Statistical Analysis

Statistical analysis was performed to establish comparisons between pre- and postoperative measurements in relation to clinical and radiological data and criteria, using the Student t test, the chi-squared test, the Mann-Whitney test, or the Fischer exact test. The Shapiro Wilk normality test was used. Survival analysis of the acetabular component was performed using the Kaplan-Meier method with radiographic data. A significant value was considered when p < 0.05, with 95% confidence interval (CI). IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

Forty patients (44 hips), with a mean follow-up of 9.65 years (2 to 18.75 years) were evaluated. In 39 initial patients of the series (88.66%), a conventional cemented acetabular component (noncrosslinked) was used.

Regarding clinical results, the mean preoperative Harris Hip Score (HHS)¹³ was 48.8 points, and in the late postoperative period it was 82. Comparatively, a statistically significant difference was observed ($p \leq 0.001$).

Of the 44 operated cases, 20 acetabular defects (45.5%) were classified as Paprosky type 3A¹⁴ and 22 (50%) as type 3B. According to the classification by D'Antonio, ¹² 39 combined defects (88.6%) were observed. The size of the bone defect in millimeters⁶ was on average 62.48 mm. The radiographic characteristics of the patients are described in ►Table 2.

The percentage of mean coverage of the implant cemented by the graft was 77% (43 to 100%), and in 41 cases (93.18%) > 50% coverage was evidenced. The largest craniocaudal thickness of the graft was on average 2.2 mm (1.2 to 4.6 mm). In 29 hips (65%), the graft configuration was classified as Prieto type 1 (footing), and in 14 (31%) as type 2 (dome support).

Postoperatively, no radiographic evidence of osseointegration was observed in 6 (13.6%) cases (Coon 3¹⁵). In 14 hips (26%), partial graft reabsorption was observed, all in DeLee zone 1.¹⁶ In 8 cases (18.2%), the presence of osteolysis was evidenced, all in DeLee zone 3.16

Progressive radiolucency lines > 2 mm wide were observed around the acetabular implant in 9 cases. Of these, in 8 cases, migration > 5 mm was evidenced. According to the radiographic criteria established, 9 cases (20.5) were considered reconstruction failures. Five (11.5%) of these patients were resubmitted to revision surgery, one of whom had an infection. Of the 9 cases of failure, no osseointegration of the graft was observed in 6 cases (Figs. 1 and 2).

Using radiographic criteria to define failure, we found a 79.54% survival rate in a mean follow-up of 9.65 years. When the criterion was used for a new surgery to review the acetabular component for any reason, survival was 88.63%. As complications, we observed 4 cases (9.09%) of instability and 1 (2.27%) of infection.

The survival of the reconstruction was evaluated through the Kaplan-Meier curve, being 92.1% in 5 years and 78.3% in 10 years, when the radiographic parameters of failure were used. The 5- and 10-year survival free of new acetabular component revision surgery for any reason as an outcome was 94.4 and 83.2%, respectively (►Fig. 3).

A correlation was observed between migration and reconstruction failure, with the absence of radiographic signs of graft osseointegration (p < 0.01). There were 5 cases with complications: 4 with instability (9.09%) and 1 (2.27%) with infection.

Discussion

In the present study, most patients had large acetabular defects; 90.9% of the defects were classified as Type III or IV of D'Antonio and 95.5% as Paprosky type 3A or 3B. A correlation was observed between reconstruction failure and absence of radiographic signs of graft osseointegration (p < 0.01). Patients with radiographic signs of failure showed significantly worse postoperative scores than the other patients.

Acetabular reconstruction in the presence of severe acetabular bone deficiency is a challenging scenario in hip revision surgery. Acetabular reconstruction techniques using structural bone graft allow restoring the center of hip rotation, obtaining implant stability, with the possibility of restoration of bone stock, facilitating future revisions.¹⁸

Acetabular reconstruction using a structural homologous graft in THAR presents controversial results in the literature. 11,18,19 Prieto et al. 2 found 94% survival in noncemented implants with high porosity metal associated with the use of structural allograft in 5 years of follow-up. Brown et al., using

Table 2 Radiographic characteristics of patients

Features		Total (n = 44)	Failure (n = 9)	Success (n = 35)	p-value	
Failure in osseointegration		62.48 (± 8.26)	65.67 (± 10.95)	61.66 (±7.39)	0.226‡	
Acetabular defect	2a	1 (2.3%)	0 (0.0%)	1 (100.0%)	0.239Δ	
(Paprosky)	2b	1 (2.3%)	1 (100.0%)	0 (0.0%)		
	3a	20 (45.5%)	4 (20.0%)	16 (80.0%)		
	3b	22 (50.0%)	4 (18.2%)	18 (81.8%)		
Acetabular defect	I	1 (2.3%)	0 (0.0%)	1 (100.0%)	0.178Δ	
(D'Antonio)	li	3 (6.8%)	0 (0.0%)	3 (100.0%)		
	lii	39 (88.6%)	8 (20.5%)	31 (79.5%)		
	lv	1 (2.3%)	1 (100.0%)	0 (0.0%)		
Coverage (%)		0.77 (± 0.16)	0.76 (±0.16)	0.78 (± 0.17)	0.748‡	
Increased graft thickness		2.20 (± 0.71)	2.30 (±0.99)	2.17 (± 0.64)	0.907‡	
Graft configuration	I (flying buttress)	29 (65.9%)	7 (24.1%)	22 (75.9%)	0.662Δ	
(Prieto)	II (dome support)	14 (31.8%)	2 (14.3%)	12 (85.7%)		
	III (footing)	1 (2.3%)	0 (0.0%)	1 (100.0%)		
Osseointegration (Coon)	1 (total)	27 (61.4%)	3 (11.1%)	24 (88.9%)	≤0.001∆	
	2 (partial)	11 (25%)	0 (0.0%)	11 (100.0%)		
	3 (away)	6 (13.6%)	6 (100.0%)	0 (0.0%)		
Migration ($\geq 2 \text{ mm}$)		9 (20.5%)	0 (0.0%)	35 (100.0%)	≤0.001¥	
Absorption (DeLee Zone I)		14 (31.8%)	5 (55.6%)	9 (25.7%)	0.117¥	
Osteolysis (DeLee Zone III)		8 (18.2%)	2 (22.2%)	6 (17.1%)	0.659¥	
Migration		8 (18.2%)	8 (88.9%)	0 (0.0%)	≤0.001¥	
Reoperation		8 (18.2%)	6 (66.7%)	2 (5.7%)	≤0.001¥	
Revision		4 (9.1%)	4 (9.1%)	0 (0.0%)	≤0.001¥	

 $\pm \mbox{Whitney U's t-test; *Student's t-test; } \mbox{\forall Fisher's Exact Test; Δ Chi-squared test.}$

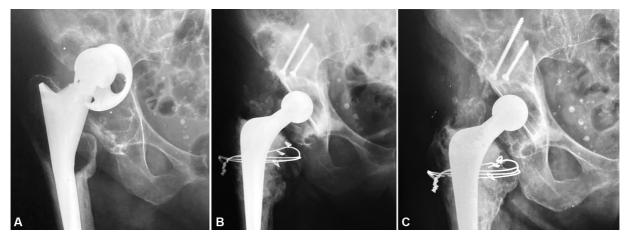


Fig. 1 Radiographs of a 73-year-old female patient who had her right hip operated. A) preoperative radiography showing noncemented total hip arthroplasty with combined defect (D'Antonio); Paprosky 3B, measuring 82 mm; B) immediate postoperative radiography presenting acetabular reconstruction with structural graft and cemented acetabular component; C) postoperative radiography at 10 years and 6 months after acetabular reconstruction without signs of release.

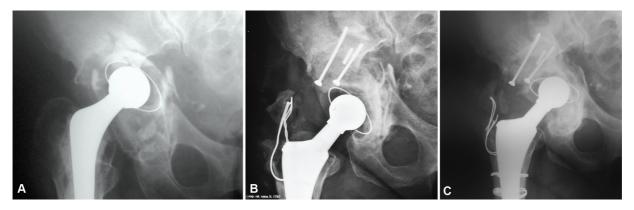


Fig. 2 Radiographs of a 63-year-old female patient who had her right hip operated. A) preoperative radiography showing cemented total hip arthroplasty with pelvic discontinuity; Paprosky 3B, measuring 80 mm; B) immediate postoperative radiography presenting acetabular reconstruction with structural graft and cemented acetabular component; C) postoperative radiography at 3 years and 1 month after acetabular reconstruction with signs of loosening.

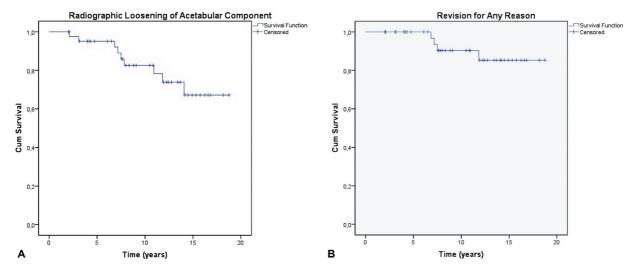


Fig. 3 Kaplan-Meier curves for reconstruction survival without revision for: (A) acetabular loosening (92.1% in 5 years, 78.3% in 10 years, and 67.5% in 15 years) or (B) any cause (94.4% in 5 years and 83.2% in 10 and 15 years).

structural allograft of distal femur associated with noncemented implant, observed 72% survival in 21 years of mean follow-up.²⁰ Garbuz et al.²¹ evaluated 33 cases of acetabular reconstruction with structural graft supporting > 50% of the implant, in a mean follow-up of 7 years. A 45% failure was observed, which occurred mainly in cases in which no reinforcement ring was used.

Butscheidt et al.,⁵ analyzed 13 structural homologous grafts after death by radiography, computed tomography (CT), histology, and electron microscopy. The distance between the current allograft and the host bone, and the distance between the original allograft and the host bone were evaluated. The study observed adequate osseointegration of all grafts along most of the interface between the graft and the host bone. The eventual nonosseointegration in some points did not lead to graft collapse within 22 years of follow-up.5

The literature indicates a higher incidence of reconstruction failure when using a structural graft with > 50% acetabular implant coverage, which we did not evidence in the present series even without the use of reinforcement

ring. 10,11,22 The patient with the longest follow-up time (18.75 years) has no signs of release or failure so far $(\succ Fig. 4).$

Total hip arthroplasty revision in the presence of severe acetabular defects is more challenging and may have worse results. In the present study, with the analysis of the treatment of large bone defects, however, we did not observe a correlation between reconstruction failure and severity of the acetabular bone defect, graft thickness or configuration.

Our study has some limitations. We observed a good time of mean follow-up of the patients (9.65 years); however, we had a considerable loss of follow-up, which made it impossible to find more conclusions. Moreover, as the series of patients is old and there was no local availability of acetabular implant cemented with crosslinked polyethylene, it should be considered that the use of conventional polyethylene in most cases may have compromised the survival of reconstruction due to early wear. We suggest future research to evaluate the osseointegration of the structural graft using only one type of cemented prosthetic implant, aiming to reduce confounding factors.

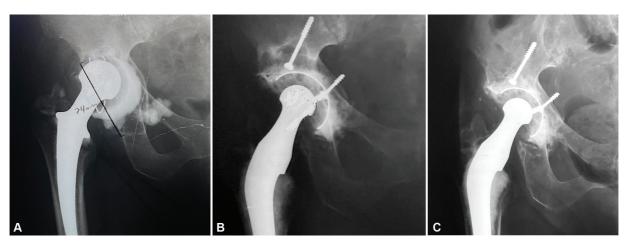


Fig. 4 Radiographs of a 74-year-old female patient who had her right hip operated. A) preoperative radiography showing cemented total hip arthroplasty with combined defect (D'Antonio); Paprosky 3A, measuring 74 mm; B) immediate postoperative radiography presenting acetabular reconstruction with structural graft and cemented acetabular component; C) postoperative radiography at 18 years and 9 months after acetabular reconstruction without signs of loosening.

Conclusion

We observed good clinic and radiographic results, with survival of 79.54% in a mean follow-up of 9.65 years. There was an association between absence of radiographic signs of osseointegration of the structural graft and failure of acetabular THAR in the present series of patients with large bone defects. The failures did not correlate with the severity of the acetabular bone defect, thickness, or graft configuration.

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Conflict of Interests

The authors have no conflict of interests to declare.

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