Acta Neurochir (2016) 158:551–556
DOI 10.1007/s00701-015-2668-1

CLINICAL ARTICLE - VASCULAR

Major recanalization occurs more often in young patients after unruptured aneurysm coil embolization

Young-Je Son[1] · O-Ki Kwon[2] · Gyojun Hwang[2] · Nam Mi Park[2] · Chang Wan Oh[2] · Jae Seung Bang[2]

Received: 9 June 2015 / Accepted: 14 December 2015 / Published online: 7 January 2016

Abstract
Background The recanalization rate after coil embolization of unruptured aneurysms was compared between young and old age groups.
Methods From May 2003 to December 2010, 636 patients with 715 saccular unruptured intracranial aneurysms (UIA) underwent endovascular coiling and were followed for at least 6 months. For comparative analysis, patients were categorized into two groups according to age 40: 42 patients with 46 aneurysms who were 40 years or younger (young age group) and 594 patients with 669 aneurysms who were older than 40 years (old age group). Angiographic and clinical outcomes including recanalization rates were compared.
Results Angiographically, class 1 or 2 occlusion according to the Raymond–Roy Occlusion Classification system was achieved in 89.2 % of the patients (91.3 % in the young age group and 89.1 % in the old age group, $p = 0.74$). Procedure-related complication rate was 2.2 % and 3.4 % in the young and the old age group ($p = 0.16$), respectively. The mean follow-up duration was 30.51 ± 18.59 months. Major recanalization occurred in seven aneurysms (15.2 %) in the young age group and in 44 aneurysms (6.6 %) in the old age group ($p = 0.03$). Retreatment was performed in seven patients (15.2 %) in the young age group and in 35 patients (5.2 %) in the old age group ($p = 0.01$).
Conclusions The present study showed that the technical feasibility and safety of endovascular coiling for UIA did not differ between the two age groups. However, the major recanalization rate was higher in the young age group.

Keywords Endovascular coiling · Recanalization · Unruptured intracranial aneurysm · Young age

Presentation at a conference: This study has not been presented in part or whole at any meeting.

✉ O-Ki Kwon
meurokwonoki@gmail.com

[1] Department of Neurosurgery, Seoul National University Boramae Medical Center, Seoul, South Korea

[2] Department of Neurosurgery, Seoul National University Bundang Hospital, 300 Gumi-dong, Bundang-gu, 463-707 Seongnam, Gyeonggido, South Korea

Introduction

A large number of unruptured intracranial aneurysms (UIA) are being increasingly diagnosed in all age groups thanks to the advances of less-invasive imaging techniques. When treatment is indicated, endovascular coiling has often been applied. In our practice, many young patients have opted for coiling as treatment for their unruptured aneurysm. It is well known that endovascular treatment has become an alternative to surgical clipping with lower morbidity and mortality rates [1–8]. However, it carries the risks of recanalization and retreatment, although surgical clipping may also suffer from the same problems. We assumed that retreatment rates in young and older patients would be similar if aneurysm and coiling factors were similar including the aneurysm size, location, and occlusion rates. A longer life expectancy could be an issue but most recanalizations occur in the early period after coiling. Therefore, if the recanalization rate for 2 or 3 years after coiling is similar regardless of the patient's age, coiling in young patients could also be an acceptable option. To the best of our knowledge, information on this issue is scarce. This study was conducted to assess the difference in the incidence of recanalization following coiling of UIA between young patients (40 years or younger) and older patients.

Methods

This retrospective study was approved by the Institutional Review Board. Clinical data such as medical records, angiographic data and other imaging studies were reviewed. From May 2003 to November 2010, 701 patients with 790 saccular unruptured intracranial aneurysms (UIA) were treated with coiling at the same center. Among them, 636 patients (167 men and 469 women) with 715 UIA (90.5 %) who were followed for at least 6 months after coiling by magnetic resonance angiography (MRA) or conventional angiography were included and analyzed in this study.

The age of the patients ranged from 10 to 85 years (mean age, 57.45 years). For comparative analysis, the patients were arbitrarily categorized into two groups: the young age group was 40 years or younger (mean age 34.26 ± 7.02 years), and the old age group was over 40 years (mean age 59.10 ± 9.19 years). The young age group included 42 patients with 46 aneurysms. The old age group included 594 patients with 669 aneurysms. The following aneurysmal characteristics were reviewed: aneurysm location, types (side wall or bifurcation), diameter (small, ≤ 5 mm; medium, 5–15 mm; large, ≥15 mm), neck size and aspect ratio and multiplicity (single or multiple). In addition, procedure-related factors, including embolization methods (single catheter, multiple catheters, balloon-remodeling, stent-assisted, combined techniques) and packing attenuation were measured and analyzed. Patient and aneurysmal characteristics are summarized in Table 1.

Endovascular embolization procedure

According to our protocol, endovascular coiling was the first-line treatment for UIA. When an aneurysm appeared to be unsuitable for coiling, surgical treatment was recommended. All aneurysm coiling was performed under general anesthesia using a biplane angiographic unit (IntegrisAllura; Philips Medical Systems, The Netherlands). Conventional coiling techniques were used and technical details have been previously reported [9, 10]. All aneurysm embolizations were performed using the following detachable platinum coils: including GDC (Boston Scientific, Fremont, CA, USA), MicroPlex (Micro-Vention, Aliso Viejo, CA, USA), Trufill-DCS (Cordis, Bridgewater, NJ, USA), and Axium (ev3, Irvine, CA, USA) coils. Modified coils, such as Matrix (Boston Scientific) and Hydrocoil (Micro-Vention), were not used. Final postembolization angiography was performed at the working projection to detect any residual contrast filling, thrombus formation, or parent artery compromise. Frontal and lateral projections were also acquired at the end of each procedure. Systemic heparinization was given after placing a femoral artery introducer sheath. In line with our protocol, 3,000 IU of heparin was administered as an intravenous bolus injection, and this was followed by an additional 1,000 IU per hour. In all patients, heparin was discontinued after embolization. Various techniques of coil embolization were used according to the morphologic characteristics of the aneurysm: single catheter technique (29.0 %), multiple catheter technique (24.8 %), balloon-assisted technique (19.6 %), stent-assisted technique (23.1 %), and multiple catheter technique in combination with a stent-assisted technique (3.6 %).

Table 1 Summary of patient and aneurysm characteristics

	Young age group (age ≤ 40 years)	Old age group (age > 40 years)	*p* value
Female	22 (52.4 %)	447 (75.3 %)	0.003
Aneurysm location			0.37
ICA	33 (71.7 %)	422(63.1 %)	
MCA	2 (4.3 %)	85 (12.7 %)	
ACA	6 (13.0 %)	97 (14.5 %)	
Posterior circulation	5 (10.9 %)	65 (9.7 %)	
Multiple aneurysm	18 (35.3 %)	271 (38.1 %)	0.76
Bifurcation type	23 (50.0 %)	480 (71.7 %)	0.004
Size			0.20
Small (≤5 mm)	30 (65.2 %)	365 (54.6 %)	
Medium (5–15 mm)	14 (30.4 %)	283 (42.3 %)	
Large and giant (≥15 mm)	2 (4.3 %)	21 (3.1 %)	
Neck size (mean mm)*	3.77 ± 1.47	4.13 ± 2.06	0.29
Aspect (dome/neck) ratio*	1.11 ± 0.53	1.25 ± 0.54	0.18

ICA internal carotid artery; *MCA* middle cerebral artery; *ACA* anterior cerebral artery

*Data are the mean ± standard deviation

The initial angiographic results were categorized using the Raymond–Roy Occlusion Classification (PROC) system as complete (class 1), residual neck (class 2), or residual aneurysm (class 3) [11].

Imaging follow-up after coil embolization

Imaging follow-up was performed using plain radiography (the same working projections as those during the coiling procedure, conventional frontal, and lateral projections), MRA or digital subtraction angiography (DSA). Our follow-up protocol is as follows: plain skull radiographs are taken at the same working projection and conventional frontal and lateral angles using the same angiographic machine at 3, 9, 15, and 21 months for detecting any changes in coil mass contour. MRAs are taken at 6, 12, and 18 months, and DSA is performed at 24 months after embolization. When the occlusion was stable and complete on the initial coiling and follow-up MRA images, we have recently replaced DSA at 24 months with MRA. MRA was then performed at intervals of 1 or 2 years thereafter according to the occlusion status. When significant coil compaction or major recanalization was suspected in noninvasive studies, a conventional catheter angiography was performed.

Recanalization

Recanalization was defined as new or increased contrast filling within aneurysms with or without aneurysm growth. Major recanalization was defined by contrast filling within the aneurysm dome, significant coil compaction, or aneurysmal regrowth. Retreatment was recommended for all patients with major recanalizations.

Statistical analysis

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Differences between patient groups were tested using the Chi-square, Fischer's exact, or Wilcoxon–Mann– Whitney test, as appropriate. Risk factors of major recanalization were analyzed by multivariate logistic regression analysis.

Results

Baseline characteristics were similar in both groups with the exception of the sex ratio and bifurcation type (Table 1). Clinical and angiographic outcomes are summarized in Table 2.

Table 2 Summary of clinical and angiographic outcomes

	Young age group (age ≤ 40 years)	Old age group (age > 40 years)	*p* value
Method			0.28
Single catheter	10 (21.7 %)	197 (29.4 %)	
Multiple catheter	10 (21.7 %)	167 (25.0 %)	
Balloon-assisted	8 (17.4 %)	132 (19.7 %)	
Stent-assisted	17 (37.0 %)	148 (22.1 %)	
Combined*	1 (2.2 %)	25 (3.7 %)	
Packing attenuation (%)**	31.66 ± 16.32	28.41 ± 14.33	0.14
Result***			0.74
Class 1	22 (47.8 %)	277 (41.4 %)	
Class 2	20 (43.5 %)	319 (47.7 %)	
Class 3	4 (8.7 %)	73 (10.9 %)	
Procedure-related adverse events			0.16
Rupture	0 (0.0 %)	1 (0.1 %)	
Thromboembolism	1 (2.2 %)	22 (3.3 %)	
Morbidity			0.38
Transient	0 (0 %)	4 (0.6 %)	
Permanent	1 (2.2 %)	0 (0 %)	

*Multiple catheter technique in combination with the stent-assisted technique

**Data are the mean ± standard deviation

***The angiographic results were classified using the Raymond–Roy Occlusion Classification (RROC) system.

Clinical outcomes

In most patients (96.8 %), coiling was performed without adverse events. Twenty-two thromboembolisms and one aneurysmal rupture occurred. These events resulted in a transient neurologic deficit in four patients (0.63 %) in the old age group and one permanent neurologic deficit in (0.16 %) in the young age group. The overall procedure-related complication rates were not significantly different between the two groups (Table 2).

Angiographic outcome

Endovascular treatment resulted in 299 (41.8 %) class 1 (47.8 % in the young age group and 41.4 % in the old age group), 339 (47.4 %) class 2 (43.5 % in young age group and 47.7 % in old age group), and 77 (10.8 %) class 3 (8.7 % in the young age group and 10.9 % in the old age group) occlusions. There were no significant differences between the two groups in terms of angiographic occlusion ($p = 0.74$).

Thirty-four aneurysms (one in the young age group and 33 in the old age group) were lost to follow-up angiography. The number of aneurysms followed for less than 6 months or lost for follow-up were 75 (four (8 %) in the young age group and 71 (9.6 %) in the old age group) ($p = 0.16$). The mean follow-

up period of the 715 aneurysms was 30.51 ± 18.5 months. There was no difference in the follow-up period between the groups; 30.76 ± 21.47 months in the young age group and 30.50 ± 18.39 months in the old group ($p = 0.92$). Follow-up angiography showed any recanalization in 12 aneurysms (26.1 %) in the young age group and in 96 aneurysms (14.3 %) in the old age group ($p = 0.05$). Major recanalization occurred in seven aneurysms (15.2 %) in the young age group and 44 aneurysms (6.6 %) in the old age group ($p = 0.03$). Among major recanalization cases, all seven aneurysms in the young age group and 35 (79.5 %) in the old age group were retreated with coiling ($p = 0.17$). Therefore, retreatment rate was 15.2 % in the young age group and 5.2 % in the old age group ($p = 0.01$), even though the recommendation to retreat was presented to all patients with major recanalization, i.e., 6.6 % in the old age group.

The time to retreatment after initial coil embolization was 9.43 ± 7.07 months in the young age group and 25.63 ± 19.87 months in the old age group ($p = 0.04$).

Multivariate logistic regression analysis showed that age of ≤40 years ($p = 0.03$; odds ratio [OR] 2.89, 95 % confidence interval [CI] 1.061–7.846), posterior circulation aneurysm ($p = 0.02$, OR 2.80, 95 % CI 1.132–6.909), medium- ($p = 0.01$, OR 2.32, 95 % CI 1.168–4.601) and large-sized aneurysms ($p < 0.001$, OR 21.00, 95 % CI 5.960–74.007) were significantly associated with major recanalization (Table 3).

Discussion

Our study shows that the durability of coiled unruptured aneurysms in young patients is lower than that in the older ones. Retreatment was performed in 15.2 % of patients in the young age group, which was almost three times higher compared to that in the old age group. Some old age group patients with major recanalization refused recoiling and the indication for retreatment may differ between the two age groups, but the major recanalization rate (6.6 %) was still less than half of that in young patients (15.2 %). There were no significant differences between the two groups with regard to most of the baseline characteristics of patients and aneurysms, except for the sex ratio and bifurcation type, but these had no significant influence on the rate of major recanalization ($p = 0.068$ and 0.332, respectively). It is well known that bifurcation type aneurysms are more prone to recanalization [12, 13]. Of note, in our series, bifurcation-type aneurysms were more prevalent in the old age group. Therefore, it does not seem to have affected our results.

Table 3 The significant risk factors of major recanalization identified by multivariate analysis (logistic regression analysis)

	p value	Odds ratio	95 % confidence interval
Age ≤ 40	0.03	2.885	1.061–7.846
Size (mm)			
5–15	0.01	2.381	1.168–4.601
≥ 15	<0.001	21.001	5.960–74.007
Location			
Posterior circulation	0.02	2.797	1.132–6.909

The results of our study are consistent with those of several other studies wherein young age was a factor for recurrence [11, 12, 14–27]. Young patients may have inherent or genetic problems in the cerebral arterial wall. No genetic studies for screening of connective tissue or hereditary diseases, which could potentially be associated with vessel wall weakness, were performed for the young age group patients in this study, but no young patients enrolled in this study reported having such diseases or a history of familial occurrence of cerebral aneurysms during medical counseling. Also, no patients showed obvious clinical or radiologic features of diseases such as fibromuscular dysplasia, coarctation of aorta, autosomal dominant polycystic kidney disease, Osler–Weber–Rendu syndrome, Ehler–Danlos type IV syndrome, or other connective tissue diseases. We assume that recanalization could be related to the different vascular elastic properties in young patients. Also, there could be some differences in the process of organized thrombus formation following intrasaccular coiling. Overall, the exact cause of the higher major recanalization rate in young patients is unclear.

Practically, higher recanalization rates in young patients should be taken into consideration when choosing treatment methods. If endovascular coiling is to be performed, angiographic follow-up will be important.

The primary goal of this study was to assess the difference in the recanalization rate between young and older patients following endovascular treatment of UIA. The results show that young patients had recanalization more often.

Nevertheless, this study has several limitations: a retrospective study design was used. Our choice of the age of 40 years was not supported by definite biologic evidence. However, we used this age criteria with reference to other medical reports and social studies [28–35]. Finally, there were relatively few patients in the young age group.

Considering the requirement of a longer follow-up period in the young age group, further studies including those with a long-term follow-up after retreatment are still necessary to characterize the efficacy and durability of endovascular treatment of UIA.

Conclusions

Endovascular treatment for UIA in the young age group was as safe as it was in the old age group. However, the recanalization rate was higher in the young age group. Posterior circulation location and aneurysmal size were also significant predictors of recanalization.

Compliance with ethical standards

Funding Seoul National University Bundang Hospital provided financial support in the form of research funding (grant no. 14-2014-002). The sponsor had no role in the design or conduct of this research.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speaker's bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

References

1. Johnston SC, Dudley RA, Gress DR, Ono L (1999) Surgical and endovascular treatment of unruptured cerebral aneurysms at university hospitals. Neurology 52:1799–1805
2. Johnston SC, Wilson CB, Halbach VV, Higashida RT, Dowd CF, McDermott MW, Applebury CB, Farley TL, Gress DR (2000) Endovascular and surgical treatment of unruptured cerebral aneurysms: comparison of risks. Ann Neurol 48:11–19
3. King JT Jr, Berlin JA, Flamm ES (1994) Morbidity and mortality from elective surgery for asymptomatic, unruptured, intracranial aneurysms: a meta-analysis. J Neurosurg 81:837–842
4. Lanterna LA, Tredici G, Dimitrov BD, Biroli F (2004) Treatment of unruptured cerebral aneurysms by embolization with guglielmi detachable coils: case-fatality, morbidity, and effectiveness in preventing bleeding–a systematic review of the literature. Neurosurgery 55:767–775
5. Raaymakers TW, Rinkel GJ, Limburg M, Algra A (1998) Mortality and morbidity of surgery for unruptured intracranial aneurysms: a meta-analysis. Stroke 29:1531–1538
6. van Rooij WJ, de Gast A, Sluzewski M, Nijssen PC, Beute GN (2006) Coiling of truly incidental intracranial aneurysms. AJNR Am J Neuroradiol 27:293–296
7. Wanke I, Doerfler A, Dietrich U, Egelhof T, Schoch B, Stolke D, Forsting M (2002) Endovascular treatment of unruptured intracranial aneurysms. AJNR Am J Neuroradiol 23:756–761
8. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC (2003) Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet 362:103–110
9. Im SH, Han MH, Kwon OK, Kwon BJ, Kim SH, Kim JE, Oh CW (2009) Endovascular coil embolization of 435 small asymptomatic unruptured intracranial aneurysms: procedural morbidity and patient outcome. AJNR Am J Neuroradiol 30:79–84
10. Kwon OK, Kim SH, Kwon BJ, Kang HS, Kim JH, Oh CW, Han MH (2005) Endovascular treatment of wide-necked aneurysms by using two microcatheters: techniques and outcomes in 25 patients. AJNR Am J Neuroradiol 26:894–900
11. Raymond J, Guilbert F, Weill A, Georganos SA, Juravsky L, Lambert A, Lamoureux J, Chagnon M, Roy D (2003) Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils. Stroke 34:1398–1403
12. Choi DS, Kim MC, Lee SK, Willinsky RA, Terbrugge KG (2010) Clinical and angiographic long-term follow-up of completely coiled intracranial aneurysms using endovascular technique. J Neurosurg 112:575–581
13. Islak C (2013) The retreatment: indications, technique and results. Eur J Radiol 82:1659–1664
14. Campi A, Ramzi N, Molyneux AJ, Summers PE, Kerr RS, Sneade M, Yarnold JA, Rischmiller J, Byrne JV (2007) Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT). Stroke 38:1538–1544
15. Cognard C, Weill A, Spelle L, Piotin M, Castaings L, Rey A, Moret J (1999) Long-term angiographic follow-up of 169 intracranial berry aneurysms occluded with detachable coils. Radiology 212:348–356
16. Grunwald IQ, Papanagiotou P, Struffert T, Politi M, Krick C, Gul G, Reith W (2007) Recanalization after endovascular treatment of intracerebral aneurysms. Neuroradiology 49:41–47
17. Hope JK, Byrne JV, Molyneux AJ (1999) Factors influencing successful angiographic occlusion of aneurysms treated by coil embolization. AJNR Am J Neuroradiol 20:391–399
18. Murayama Y, Nien YL, Duckwiler G, Gobin YP, Jahan R, Frazee J, Martin N, Vinuela F (2003) Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg 98:959–966
19. Nguyen TN, Hoh BL, Amin-Hanjani S, Pryor JC, Ogilvy CS (2007) Comparison of ruptured vs unruptured aneurysms in recanalization after coil embolization. Surg Neurol 68:19–23
20. Pandey AS, Koebbe C, Rosenwasser RH, Veznedaroglu E (2007) Endovascular coil embolization of ruptured and unruptured posterior circulation aneurysms: review of a 10-year experience. Neurosurgery 60:626–636
21. Pierot L, Delcourt C, Bouquigny F, Breidt D, Feuillet B, Lanoix O, Gallas S (2006) Follow-up of intracranial aneurysms selectively treated with coils: Prospective evaluation of contrast-enhanced MR angiography. AJNR Am J Neuroradiol 27:744–749
22. Raymond J, Chagnon M, Collet JP, Guilbert F, Weill A, Roy D (2004) A randomized trial on the safety and efficacy of endovascular treatment of unruptured intracranial aneurysms is feasible. Interv Neuroradiol 10:103–112
23. Shankar JJ, Lum C, Parikh N, dos Santos M (2010) Long-term prospective follow-up of intracranial aneurysms treated with endovascular coiling using contrast-enhanced MR angiography. AJNR Am J Neuroradiol 31:1211–1215
24. Slob MJ, Sluzewski M, van Rooij WJ (2005) The relation between packing and reopening in coiled intracranial aneurysms: a prospective study. Neuroradiology 47:942–945
25. Sluzewski M, Menovsky T, van Rooij WJ, Wijnalda D (2003) Coiling of very large or giant cerebral aneurysms: long-term clinical and serial angiographic results. AJNR Am J Neuroradiol 24:257–262

26. Sluzewski M, van Rooij WJ, Rinkel GJ, Wijnalda D (2003) Endovascular treatment of ruptured intracranial aneurysms with detachable coils: long-term clinical and serial angiographic results. Radiology 227:720–724
27. Tamatani S, Ito Y, Abe H, Koike T, Takeuchi S, Tanaka R (2002) Evaluation of the stability of aneurysms after embolization using detachable coils: correlation between stability of aneurysms and embolized volume of aneurysms. AJNR Am J Neuroradiol 23: 762–767
28. Hart R, Miller V (1983) Cerebral infarction in young adults: a practical approach. Stroke 14:110–114
29. Honda A, Tanabe N, Seki N, Ogawa Y, Suzuki H (2014) Underweight/overweight and the risk of long-term care: Follow-up study using data of the Japanese long-term care insurance system. Geriatr Gerontol Int 14:328–335
30. Klein LW, Agarwal JB, Herlich MB, Leary TM, Helfant RH (1987) Prognosis of symptomatic coronary artery disease in young adults aged 40 years or less. Am J Cardiol 60:1269–1272
31. Lee T-H, Hsu W-C, Chen C-J, Chen S-T (2002) Etiologic study of young ischemic stroke in Taiwan. Stroke 33:1950–1955
32. O'Connell JB, Maggard MA, Livingston EH, Yo CK (2004) Colorectal cancer in the young. Am J Surg 187:343–348
33. Thompson RH, Ordonez MA, Iasonos A, Secin FP, Guillonneau B, Russo P, Touijer K (2008) Renal cell carcinoma in young and old patients—is there a difference? J Urol 180:1262–1266
34. Zimmerman FH, Cameron A, Fisher LD, Grace N (1995) Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). J Am Coll Cardiol 26:654–661
35. Bollet MA, Sigal-Zafrani B, Mazeau V, Savignoni A, de la Rochefordière A, Vincent-Salomon A, Salmon R, Campana F, Kirova YM, Dendale R (2007) Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first. Radiother Oncol 82:272–280