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CLINICAL TRIAL

Meta-analysis of upgrade rates in 3163 radial scars excised after needle core biopsy diagnosis

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Abstract

Background Since concurrent malignancy may be associated with radial scars (RS) in up to 45% of RS diagnosed on core biopsy, surgical excision is usually advised. Recent very low upgrade rates have caused a re-evaluation of the need for routine surgery. We aimed to find subsets of RS at such low risk of upgrade, as to render imaging surveillance a plausible alternative to surgery.

Design We performed a systematic review of the Pubmed, Cochrane and Embase databases, focusing on the following eligibility criteria: full papers, published after 1998, in English, included at least 5 RS, provided information on needle biopsy gauge and upgrade rates based on the excised lesion. For the meta-analysis, studies were grouped by the presence of histologic atypia and the core needle gauge. Study-specific and pooled upgrade rates were calculated for each subgroup.

Results 49 studies that included 3163 RS with surgical outcomes are included. There were 217 upgrades to malignancies, 71 (32.7%) invasive and 144 (66.4%) DCIS. The random-effects pooled estimate was 7% (95% CI 5, 9%). Among the pre-planned subgroups, in RS assessed by 14G NCB the upgrade rates were: without atypia − 5% (95% CI 3, 8%), mixed or presence of atypia not specified − 15% (95% CI 10, 20%), with atypia − 29% (95% CI 20, 38%). For RS assessed by a mix of 8-16G cores the respective upgrade rates were 2% (95% CI 1, 4%), 12% (95% CI 6, 18%) and 11% (95% CI 3, 23%) and for RS assessed by 8–11 vacuum assisted biopsies 1% (95% CI 0, 4%), 5% (95% CI 0, 11%) and 18% for the one study of RS with atypia assessed by VAB. Surgery after VAB excision showed no upgrades. The difference across all subgroups was statistically significant.

Conclusion When stratified by atypia and biopsy gauge, upgrade rates in RS are consistent and predictable. RS assessed by VABs and lacking atypia have a 1% (95% CI 0, 4%) upgrade rate to DCIS. Other groups have upgrade rates of 2–28%. This risk may be reduced by VAB excision. The results of this meta-analysis provide a decision aid and evidence-based selection criteria for surgery after a needle biopsy diagnosis of RS.

Keywords Radial scar · Breast cancer · Screening · Mammography · Core biopsy

Introduction

Since the turn of this century, NCBs have become the first line diagnostic modality for the histologic evaluation of breast lesions found on imaging. Their simplicity and close correlation with the final histology have reduced substantially the reliance on surgical biopsies. However, for several specific subsets of breast lesions, such as radial scars, core biopsies may not be fully representative of the entire process, such that immediate surgical excision discovers unsuspected concurrent invasive cancer or DCIS in over 40% of the cases. Atypical ductal hyperplasia, lobular carcinoma *in situ*, atypical lobular hyperplasia, papillary lesions, radial scars, cellular fibroepithelial lesions and flat epithelial atypia are among the diagnoses which when made on a needle core biopsy

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(NCB) have been associated with significant upgrade rates, leading to the standard recommendation for diagnostic surgical biopsy. The upgrade rates vary among these lesions, ranging from < 10% for radial scars and fibroepithelial lesions to > 40% for ADH. Although well intentioned and justified, the fact remains that for most women such surgery finds no malignancy. Attempts at finding subsets of women whose likelihood of an upgrade is sufficiently low as to forego surgical biopsy have had variable success and are ongoing.

Radial scars (RS) are benign, mostly asymptomatic breast lesions, common in well women. Because their spiculated outline on mammograms simulate invasive cancer, they are frequently evaluated after mammographic screening, where their prevalence is 5–6 per 10,000 mammograms [3, 22]. RS are diagnosed in 1–3.7% of core biopsies [18, 20] and account for 10% of all lesions undergoing diagnostic open biopsy [2, 11]. The detection of RS is expected to increase with the greater use of digital breast tomosynthesis, due to its improved visualization of architectural distortions [9, 24].

In a recent analysis of contemporary indications for open biopsy after screening [11], we found that while RS has a relatively high prevalence of 10%, its upgrade rate was only 12.2%, implying that the identification of effective risk stratification strategies for RS has the potential to have a significant impact in reducing benign open biopsies.

Even contemporary reports of upgrade rates for RS have varied substantially, ranging from 0 to 28% [27]. This, combined with the lack of reliable predictive imaging characteristics of focal malignant change in RS, [15] has led to variation in practice, most centres recommending conservative surgical excision of RS diagnosed on NCB, while some now advocate observation [8–10].

Aims

We wished to identify subsets of women with a NCB diagnosis of RS who may safely avoid surgery. We hypothesised that much of the variance in the published estimates for upgrades of RS would be resolved if outcomes were stratified by the presence of atypia and the needle gauge of the core biopsy, as a surrogate for the extent of NCB sampling.

Materials and methods

Literature search and eligibility criteria

Using search terms "radial scar" or "complex sclerosing process" AND "breast" a search of the PUBMED, Embase and Cochrane databases was performed in September 2017 and repeated in October 2018 to identify primary studies that met pre-defined eligibility criteria, as follows: full papers, published after 1998, in English, included at least 5 RS diagnosed on NCB, provided information on biopsy gauge and upgrade rates of the excised lesion.

Study endpoints

The primary endpoint for this meta-analysis was the diagnosis based on pathologic evaluation of the excised lesion. Only invasive carcinoma or DCIS were included in the upgrade rate. As the principal decision being faced after a NCB diagnosis of RS is whether the area should be excised or not, we were only interested in conditions managed surgically. As such, lobular carcinoma *in situ*, atypical ductal hyperplasia or flat epithelial atypia were not included in the calculation of upgrade rates.

Extracted data

Study-specific descriptive information (clinical context, year of publication, country of origin) and quantitative data were extracted. This included the total number of RS diagnosed by NCB, the number of RS undergoing surgical excision, the needle gauge used for NCB and number of cores retrieved. For the subset of excised RS, the number showing histologic atypia on the NCB and the surgical pathology results, classified as the number of invasive cancers, DCIS or non-malignant findings were recorded. The presence of atypia, or lack thereof, was drawn directly from each study. If the study did not specify the presence of atypia or grouped all RS, the grouping "presence of atypia not specified or mixed results" was used. Information regarding needle gauge was drawn directly from each series. For studies that did not specify this information, the range of needle gauges used was used. When the same study presented data for RS assessed by various needle gauges or with varying histologic findings on NCB, the data were tabulated separately for each subset.

To address the heterogeneity in study designs, the findings were grouped into the following categories: (1a) RS assessed by 14G NCB, without atypia, (1b) RS assessed by 14G NCB, presence of atypia not specified or mixed results, (1c) RS assessed by 14G NCB, with atypia, (2a) RS assessed by a mix of 8-16G NCB, without atypia, (2b) RS assessed by a mix of 8-16G NCB, presence of atypia not specified or mixed results (2c) RS assessed by a mix of 8-16G NCB, with atypia, (3a) RS assessed by VAB 8-11G biopsies, without atypia, (3b) RS assessed by VAB 8-11G biopsies, presence of atypia not specified or mixed results, (3c) RS assessed by VAB 8-11G biopsies, with atypia, (4) RS undergoing surgery after VAB excision and (5) RS assessed by MRI guided 9-G VA biopsies.

We also evaluated series dealing with three special case scenarios, too few for meta-analysis, but nevertheless of practical, clinical interest. These included (i) RS ≤ 5 mm,

without atypia or a papillary component, (ii) "Microscopic RS" defined as RS as an incidental histologic finding during evaluation of another target lesion with concordant imaging and (iii) "Mammographically occult RS" assessed by ultrasound guided 14-G NCB.

Statistical methods

Random-effects meta-analysis of proportions used the Der Simonian and Laird method to pool prevalence of upgrade to invasive carcinoma or DCIS following Freeman-Tukey Double arcsine transformation. Study upgrade rates were calculated using the number of lesions with malignant surgical outcomes and the number of women who underwent surgical biopsy as the denominator. The meta-analysis was stratified according to the subgroups described above and tests and measures of heterogeneity within and across subgroups were calculated. All summary measures (subgroup and overall) were reported with 95% exact confidence intervals.

We used Stata version 14.2 (StataCorp 2009; College Station, TX) for meta-analysis and the user written module metaprop.

Results

Our search strategy identified 271 citations; reduced to 88 by screening of titles. Review of abstracts and the full paper identified 51 papers as meeting eligibility criteria. These included 8 studies based solely on organised population-based screening programs. Combined, the eligible studies presented data for 3163 RS excised after NCB. The QUOROM diagram and Prisma checklist for this review are available in the appendix as supplementary information.

Overall, concurrent malignancy was documented in 217 cases (raw average 6.9%), of which 71 (32.7%) were invasive cancers and 144 (66.4%) DCIS (Table 1). The reported upgrade rates spanned a range of 0–45.4%.

Table 1 Series of RS with excision outcomes included in this meta-analysis

Study	Year	Context	RS on NCB	RS excised	Upgrade to invasive cancer	Upgrade to DCIS	% Malignant upgrade rate	Number of cores
1. RS diagnosed on 14G NCB								
1a. RS diagnosed on 14G NCB–without atypia								
Jackman	1999	US		5	0	2	40	Unknown
Kirwan	2000	UK		30	0	0	0.0	9
Philpotts	2000	US	9	8	0	0	0.0	2–10, mean 8.1
Cawson	2003	Australia. Screening	54	54	0	1	1.9	2–12, median 5
Lee	2003	UK	20	15	0	1	6.7	Unknown
Brodie	2004	Ireland. Screening	16	16	0	2	12.5	3–9, average 4
Becker	2006	US		50	NS	NS	8.0	Average: 6.1
Douglas-Jones	2007	Wales. Screening	289	289	5	6	3.9	Unknown
El-Sayed	2008	UK. Screening		132	6	6	9.1	Unknown
Hayes	2009	Ireland. Screening		42	0	4	9.5	Unknown
Linda	2010	Italy		43	2	2	9.3	3–8, mean 5
Osborn	2011	Wales. Screening	95	95	4	3	7.4	1–10, median 3
Londero	2011	Italy	88	NS	NS	NS	6.0	Ultrasound cores range 4–7, mean 5. Stereotactic cores range 6–18, mean 12
Bianchi	2012	Italy		49	1	3	8.2	3–8, mean 4
Total				828	18	30	5.80	
1b: RS diagnosed on 14G NCB–presence of atypia not specified or mixed								
Lopez-Medina	2006	Spain	52	43	6	2	18.6	5–9, mean 6.4
Farshid	2017	Australia. Screening	82	80	5	5	12.5	Mode: 3
Ferreira	2017	Portugal	88	78	5	7	15.4	Median: 6
Total				201	16	14	14.9	

Table 1 (continued)

Study	Year	Context	RS on NCB	RS excised	Upgrade to invasive cancer	Upgrade to DCIS	% Malignant upgrade rate	Number of cores
1c: RS diagnosed on 14G NCB–with atypia								
Kirwan	2000	UK		11	1	4	45.4	9
Lee	2003	UK	10	9	1	3	44.4	Unknown
Becker	2006	US		24	NS	NS	25.0	14G: Average: 6.1
Dillon	2007	Ireland	22	19	1	6	36.8	3 for us guided biopsies. For stereo cores (14 or 11G) 8 samples
El-Sayed	2008	UK. Screening		21	1	4	23.80	Unknown
Hayes	2009	Ireland. Screening		15	0	3	20.0	Unknown
Osborn	2011	Wales. Screening	15	15	1	2	20.0	1–10, median 3
Total				114	5	22	23.7	
2. RS diagnosed on a mix of 8-16G NCB								
2a: RS diagnosed on a mix of 8-16G NCB–without atypia								
Philpotts	2000	US	9	8	0	0	0	2–120, mean 8.1
Brenner	2002	US	128	73	2	2	5.50	Stereotactic spring loaded biopsy: 3–20, median 7; stereotactic VAB: 4–38, median 14; sonographic spring loaded biopsy 2–14, median 5; sonographic VAB 5–24 median 15
Dillon	2007	Ireland	41	35	0	2	5.7	3 for ultrasound guided biopsies. For stereo cores (14 or 11G) 8 samples
Londero	2011	Italy	88	NS	NS	NS	4	Ultrasound cores range 4–7, mean 5. Stereotactic cores range 6–18, mean 12
Rakha	2011	UK	39	36	0	1	2.8	Unknown
Miller	2014	US		102	1	1	1.9	14G ultrasound guided biopsies: 5 cores; 7-11G VAB: 4–6 cores
Dominguez	2015	Itlay	51	42	1	6	16.7	NCB: 2–5, mean 3, VAB: 7–12, mean 10 cores
Hou	2016	US	81	40	0	0	0	3–5 passes
Li	2016	US	403	220	1	1	0.9	Ultrasound 14G cores range 3–5. Stereotactic or MR 9G cores range 6–9
Leong	2016	US	292	161	0	1	0.6	Ultrasound 14-16G cores at least 3 cores. Stereotactic or MR 9G biopsies generally 12 cores

Table 1 (continued)

Study	Year	Context	RS on NCB	RS excised	Upgrade to invasive cancer	Upgrade to DCIS	% Malignant upgrade rate	Number of cores
Donaldson	2016	US	57	37	0	0	0	At leas 6–12
Kim	2016	US	88	63	0	1	1.6	On average 4–6 samples
Kalife	2016	US, incidental RS	54	14	0	0	0	Ultrasound: 5, stereo: 6, MR: 8
Kalife	2016	US, Targeted RS	46	27	0	0	0	Ultrasound: 5, stereo: 6, MR: 8
Mooney	2016	US	54	25	1	3	16	Unknown
Mesa-Quesada	2017	Spain	54	12	0	0	0.00	Ultrasound: 3–6, stereo VAB: 12
Nakhlis	2018	US	118	34	1	2	8.80	Unknown
Phantana-angkool	2018	US, included DBT		223	2	6	3.60	Unknown
Lamb	2018	US, included DBT		111	1	3	3.60	Unknown
Total				1263	10	29	2.90	
2b: RS diagnosed on a mix of 8-16G NCB–presence of atypia not specified or mixed								
Houssami	2007	Italy		42	3	4	16.70	Unknown
Flegg	2010	Australia. Screening	18	18	0	0	0.00	Unknown
Andacoglu	2013	US		67	0	4	5.90	Range 4–12
Nassar	2015	US	100	38	2	2	10.40	> 4 in 83%
Dominguez	2015	Itlay	25	25	3	5	32	NCB: 2–5, mean 3, VAB: 7–12, mean 10 cores
Hoffmann	2016	Germany. Screening		15	1	3	27	NCB: 4, VAB: 12
Chou	2018	US	18	18	1	0	5.60	Unknown
Richter-Ehrenstein	2018	Germany. Screening	27	20	3	1		14G ultrasound: 3–5, 11G VAB: 12–16
Total				243	10	19	12.60	
2c: RS diagnosed on a mix of 8–16G NCB–with atypia								
Brenner	2002	US	29	29	3	5	27.50	Stereotactic spring loaded biopsy: 3–20, median 7; stereotactic VAB: 4–38, median 14; sonographic spring loaded biopsy 2–14, median 5; sonographic VAB 5–24 median 15
Dillon	2007	Ireland	22	19	1	6	36.80	3 for ultrasound guided biopsies. For stereo cores (14 or 11G) 8 samples
Rakha	2011	UK	4	3	0	0	0	Unknown
Miller	2014	US		22	0	3	13.60	14G ultrasound guided biopsies: 5 cores; 7-11G VAB: 4–6 cores

Table 1 (continued)

Study	Year	Context	RS on NCB	RS excised	Upgrade to invasive cancer	Upgrade to DCIS	% Malignant upgrade rate	Number of cores
Leong	2016	US		54	2	4	11.1	Ultrasound 14-16G cores at least 3 cores. Stereotactic or MR 9G biopsies generally 12 cores
Mesa-Quesada	2017	Spain	18	18	1	0	5.60	Ultrasound: 3–6, stereo VAB: 12
Chou	2018	US	31	26	0	0	0	Unknown
Total				171	7	18	14.60	
3. RS diagnosed on VAB 8-11G biopsies								
3a: RS diagnosed on VAB 8-11G biopsies–without atypia								
Becker	2006	US		9	0	0	0	Average: 32.1
Resetkova	2008	US	80	19	0	0	0	11G VAB: 12, ±4; 9G VAB: 9, ±3
Sohn	2010	US	38	27	0	0	0	Range 4–12
Linda	2010	Italy		19	0	1	5.30	9–18, mean 12
Conlon	2015	US	53	48	0	1	2.10	Unknown
Total				122	0	2	1.60	
3b: RS diagnosed on VAB 8-11G biopsies–presence of atypia not specified or mixed								
Resetkova	2008	US	80	19	0	0	0	11G VAB: 12, ±4; 9G VAB: 9, ±3
Morgan	2012	US		67	2	4	9.00	Unknown
Saladin	2016	Switzerland	113	18	NS	NS	11.10	Average: 14
Ferreira	2017	Portugal	25	11	0	0	0	Median 6
Total				115	2	4	5.2	
3c: RS diagnosed on VAB 8-11G biopsies–with atypia								
Becker	2006	US	12	11	NS, "2 malignant"	NS, "2 malignant"	18.2	Average: 32.1
4. RS surgically excised after undergoing VAB excision								
Becker	2006	US	36	27	0	0	0	Average: 32.1
Tennant	2008	UK		18	0	0	0	Unknown
Rajan	2011	UK		12	0	0	0	3G VAB: 10–24, mean 18; 11G VAB: 18–48, mean 28
Total				57	0		0	
5. RS diagnosed on MRI guideded 9G biopsy								
Heller	2014	US		25	2	4	24	10–12 cores
Lourenco	2014	US	20	13	1	2	23.1	Minimum of 6
Total				37	3	6	24.3	

Considering the entire cohort, as displayed in Fig. 1, there was evidence of significant heterogeneity between the groups ($p = 0.000$). This confirms there is likely to be significant variability between the studies overall, rendering a pooled analysis inappropriate. Study design and patient numbers varied among the studies. Study-specific data, upgrade rates, and estimated pooled upgrade rates, are displayed in Fig. 1.

Within each subgroup and sorted in chronological order, a trend appeared towards lower upgrade rates in more recent series, possibly reflecting more comprehensive sampling over time.

Table 2 presents the raw numbers of cases used in this analysis, stratified by the planned subtypes. The number of series contributing to each sub-group are: 24 for RS assessed by 14G NCB, 33 for RS assessed 8-16G biopsies, 10 for RS

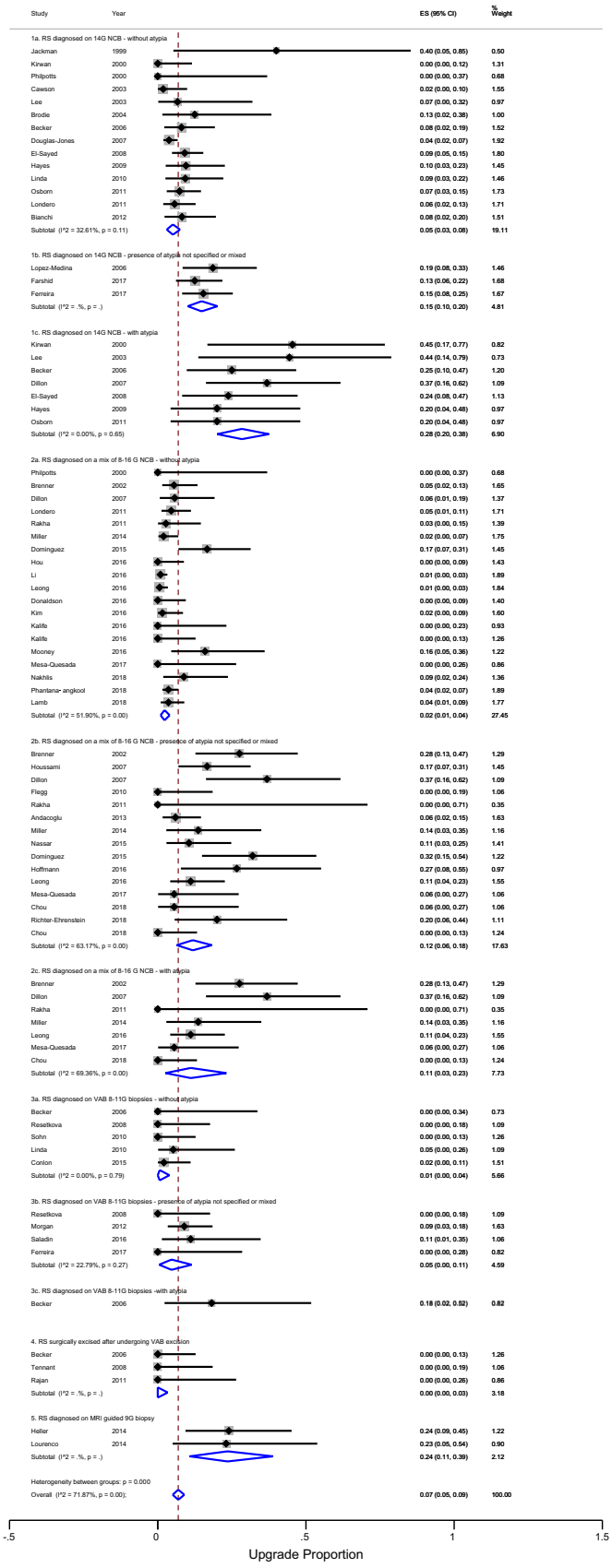

Fig. 1 Overall meta-analysis results of radial scars excised after core biopsy. *ES* effect size. This is the malignant upgrade rate, expressed as a proportion. % weight = random effects weights applied to each study in the overall meta-analysis. The studies are grouped by the gauge of the core biopsy needle used (14G, mix of 8-16G and vacuum assisted biopsies 8-11G). Within each group, studies are stratified as follows: no atypia, presence of atypia not specified or mixed results and atypical. Two further groups are also included: RS proceeding to surgical exsion after a VAB excision and RS evaluated under MRI guidance by 9G VAB. All subgroups are listed in chronological order of year of publication. The diamonds at the end of each section represent the pooled estimates of upgrade for the subgroup of radial scars according to the meta-analysis with 95% confidence interval also being presented. While the overall pooled estimate of upgrade for all studies combined is 7%, (95% confidence interval 6, 9%), grouping by needle gauge and presence of atypia stratifies the cases into subsets with significantly different upgrade rates. A measure of heterogeneity (I^2) is provided by subgroup where there are > 3 studies, and overall

Table 2 Numbers of radial scars and outcome, stratified by RS subgroup

Subgroup	Studies included	Excised RS	Upgrade to invasive cancer	Upgrade to DCIS	Total malignant lesions	Raw average upgrade (%)	Pooled estimate of upgrade (95% confidence interval)
1. RS diagnosed on 14G NCB							
1a. No atypia	14	828	18	30	48	5.8	5% (3, 8%)
1b. Presence of atypia not specified or mixed	3	201	16	14	30	14.9	15% (10, 20%)
1c. With atypia	7	114	5	22	27	23.7	28% (20, 38%)
2. RS diagnosed on a mix of 8-16G NCB							
2a. No atypia	19	1263	10	29	39	3.9	2% (1, 4%)
2b. Presence of atypia not specified or mixed	7	243	10	19	29	11.9	12% (6, 18%)
2c. With atypia	7	171	7	18	25	14.6	11% (3, 23%)
3. RS diagnosed on VAB 8-11G biopsies							
3a. No atypia	5	122	0	2	2	1.6	1% (0, 4%)
3b. Presence of atypia not specified or mixed	4	115	2	4	6	5.2	5% (0, 11%)
3c. With atypia	1	11	NS	NS	2	18.2	Only 1 study
4. RS surgically excised after VAB excision	3	57	0	0	0	0	0% (0, 3%)
5. RS diagnosed on MRI guided 9G biopsy	2	38	3	6	9	23.7	24% (11, 39%)
Total		3163	71	144	217	6.90	

assessed by 8-11G VABs, 3 for RS undergoing surgery after prior VAB excision and 2 for RS assessed by MRI guided VABs. Several series presented data for more than one pre-planned category.

Of the special subtypes, one study of each of the following groups was found: RS ≤ 5 mm without atypia [19]; mammographically occult, asymptomatic RS, found only on ultrasound without atypia [23] and microscopic or incidental RS [16], together representing an additional 103 RS.

A grand total of 3266 excised RS is therefore included in this evaluation.

Modelled estimates

Table 3 and Fig. 2 summarise the surgical outcomes in women with RS stratified by needle gauge and the presence of atypia. For women with RS assessed by 14G NCB, the meta-analysis includes 1143 RS presented in 24 studies. The pooled estimate of upgrade was 5% (95% CI 3%, 8%) without atypia, 15% (95% CI 10%, 20%) when the presence of atypia was not specified and 28% (95% CI 20%, 38%) when atypia was identified on the NCB. Please note, the upgrade rates in the meta-analysis are not the same as the averages of the raw data, because weights are applied to each study in a meta-analysis.

For women with RS assessed by a mix of 8-16G NCB, the meta-analysis includes 1991 RS presented in 21 studies. The pooled estimate of upgrade was 2% (95% CI 1%, 4%) without atypia, 12% (95% CI 6%, 18%) when the presence of atypia was not specified and 11% (95% CI 3%, 23%) when atypia was identified on the NCB.

For women with RS assessed by 8-11G VAB, the meta-analysis includes 248 RS presented in 10 studies. The pooled estimate of upgrade was 1% (95% CI 0%, 4%) without atypia, 5% (95% CI 0%, 11%) when the presence of atypia was not specified and 18% in the one study when atypia was identified on the NCB (not listed in the meta-analysis, as a single study).

Table 3 Pooled estimated upgrade rates for each planned subgroup of RS

Pooled estimated upgrade rates					
	Number of RS	Series included	RS without atypia	RS, atypia not specified	RS with atypia
RS diagnosed on 14G NCB	1143	24	5% (3, 8%)	15% (10, 20%)	28% (20, 38%)
RS diagnosed on a mix of 8-16G NCB	1677	33	2% (1, 4%)	12% (6, 18%)	11% (3, 23%)
RS diagnosed on VAB 8-11G biopsies	248	10	1% (0, 4%)	5% (0, 11%)	18%
RS surgically excised after VAB excision	57	3	–	0% (0, 3%)	–
RS diagnosed on MRI guided 9G biopsy	38	2	–	24% (11, 39%)	–

Please note, as weights are applied in a meta-analysis, the pooled estimates are different from the raw average of all studies combined

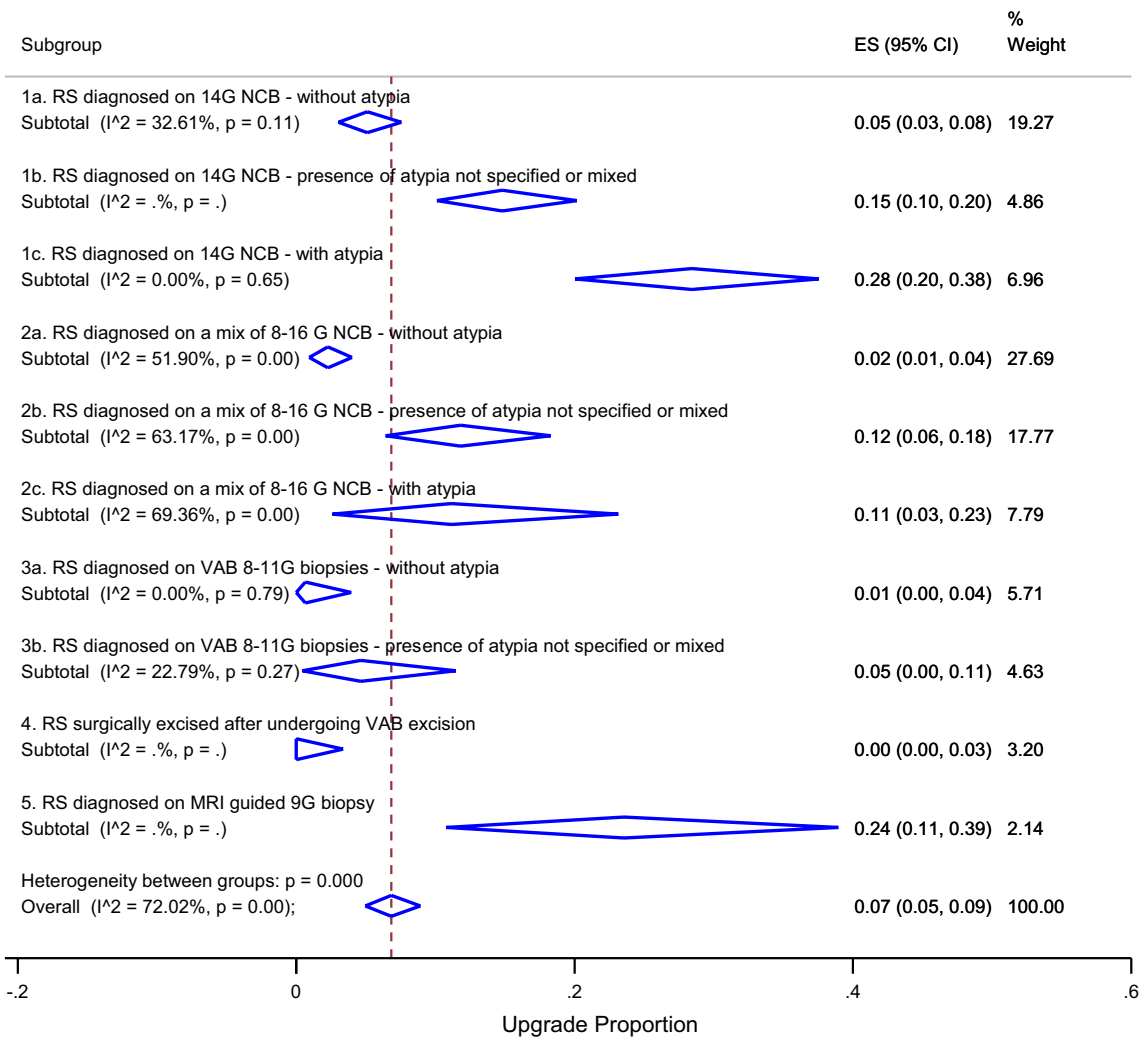

Fig. 2 Summary of proportion of malignant upgrades for each subgroup of radial scars. *ES* effect size (the upgrade rate expressed as a proportion), % weight = random effects weights. This plot presents the pooled estimates of upgrade and 95% confidence intervals for each subgroup of RS and also the overall upgrade rate, presented in Fig. 1. Heterogeneity (I^2) is statistically significant across all subgroups (71.5%, $p < 0.001$). As subgroup 3c included only one study, summary analysis is not applicable

Table 3 and Fig. 2 also present the surgical outcomes for women undergoing surgery after VAB excision of RS. The presence of atypia in the VAB excision was not specified. The meta-analysis includes 57 such RS, presented in 3 studies. No upgrades were found in any of these 3 series (95% CI 0%, 3%).

The two series of RS evaluated by MRI guided biopsies, mostly by VABs, showed a pooled upgrade rate of 24% (95% CI 11, 39%).

Overall, there is a statistically significant difference across subgroups ($p < 0.001$). Within the subgroup assessed by 14G NCB, there was a statistically significant difference between the outcomes when stratified by the presence of atypia, as evident by the absence of overlapping confidence intervals. This is also true for RS assessed by 8-16G biopsies without atypia, versus those with atypia, but the more heterogeneous subgroup assessed by 8-16G biopsies shows overlapping confidence intervals with both other subgroups. For RS assessed by 8-11G VABs, the upgrade rate for several studies was zero, regardless of whether atypia was present or not specified. It is therefore unlikely that a statistically significant difference between such subgroups would be detected.

As shown in Table 4, Among the special case scenarios, for which relatively fewer cases have been reported, no upgrades were recorded in the following groups: RS ≤ 5 mm lacking atypia or an accompanying papillary component, "microscopic" RS found incidentally on histology when another lesion was targeted and successfully biopsied, and finally, in mammographically occult RS, found only on ultrasound examinations.

Table 4 Special case scenarios of radial scars diagnosed on core biopsy

	Number of RS included	Number of studies	Upgrade rate (%)
RS ≤ 5 mm, without atypia or a papillary component	77	1	0
Microscopic RS, Incidental histologic finding during evaluation of another target lesion	18	1	0
Mammographically occult RS assessed by US guided 14-G NCB	8	1	0

Discussion

Practice patterns for biopsy and management of RS are evolving. Whereas early series reported malignant upgrades in 25–45% of RS, some recent series have found far lower upgrades. Already one of the common borderline lesions, the detection of RS is likely to increase further with the growing use of tomosynthesis, providing further interest in non-surgical management of these lesions [24]. However, the wide range of reported upgrade rates, the persistence of a significant risk of undiagnosed malignancy even in contemporary practice and the lack of predictive imaging characteristics of foci of malignant change pose formidable barriers to the routine non-surgical management of RS.

We have focused on atypia and the extent of sampling as two plausible factors to account for the substantial variation in reported upgrade rates. Our meta-analysis of 49 series captures data for 3163 women, evaluated in the planned subgroup analysis. When stratified according to these key variables, the estimates for upgrade rates are more consistent within each subgroup, than in the whole dataset and statistically significant differences in the upgrade rates are evident. Within the subset assessed by 14G NCB, the presence of atypia is confirmed as a significant predictor of a malignant upgrade. Some heterogeneity remains among RS without atypia assessed by 14G NCB, the chief outlier being the series by Jackman in 1999, with a 40% upgrade rate, likely due to the small sample size of only 5 cases. As expected, there remains significant heterogeneity within the subgroup assessed by 8-16G NCBs, this group capturing a diverse mix of biopsy modalities. The upgrade rates were significantly lower for the group assessed by the 8-11G VABs than those assessed by smaller biopsies, but the low upgrade rates among all subsets of this group preclude assessment of the impact of histologic atypia.

Outside of intentional VAB excisions, the group with the lowest upgrade rate is RS without atypia assessed by VA biopsies. The upgrade rate for this group was 1% (95% CI 0–4%), comprising two cases of DCIS among 122 lesions.

The next lowest upgrade rate of 2% (95% CI 1–4%) was among RS without atypia sampled via 8-16G NCB. This group comprised 1263 RS, amongst which on excision 29 cases of DCIS and 10 invasive cancers were documented.

Two subgroups each had upgrade estimates of 5%. These included (i) RS without atypia assessed by conventional 14G NCB that included 30 cases of DCIS and 18 invasive cancers among 828 RS; and (ii) RS assessed by VAB, when the presence of atypia was not specified, comprising of 4 cases of DCIS and 2 invasive cancers among 115 RS.

Among RS without atypia, there was a small but step wise decline in upgrade rates with increasing needle gauge, with an upgrade of 5% (95% CI 3, 8%) among RS assessed by 14G cores to 2% (95% CI 1, 4%) for those assessed by 8-16G NCB and 1% (95% CI 0, 4%) for VABs. As discussed above, RS assessed by a mix of 8-16G needle biopsies also had a low upgrade of 5% (95% CI 0, 11%).

In all other subgroups, the upgrade estimates exceeded 10% and were as high as 28% when sampled via 14G cores and showed atypia. The upgrades in all these groups included invasive cancers as well as DCIS.

Concurrent malignancy in a RS may be focal and the correlation of extent of sampling with upgrade rates has been noted previously [15]. Because VABs produce larger volume samples, they lessen the potential for under sampling and diagnostic errors. Among other borderline lesions, the use of VABs has decreased the underestimation of ADH and DCIS [6, 13, 25]. Our analysis now confirms its improved sensitivity for the evaluation of RS. The present conclusions are concordant with previous reports emphasising the correlation between upgrade rates and biopsy modality, extent of sampling (> 12 cores), radiology pathology concordance and absence of atypia [5, 22, 29]. We note significant disparity among the studies in the number of core samples retrieved, ranging from 1 to 32.1 and up to 48 for VAB excision [28]. While data on the number of cores retrieved are not available for several series, in general, mores samples are obtained from VA biopsies. The larger gauge of the VAB excisions, combined with the greater number of samples lead to a larger proportion of lesions being evaluated by VABs, leaving less of the lesion unexamined. This more comprehensive evaluation reduces the chances of an upgrade on excision. Our findings are consistent with Ferreira's 2017 logistic regression [12]. They reported that the use of VAB reduced the upgrade rate by 87%, or 3 times less than that of 14G NCB. They also found the presence of atypia was the only significant predictor of malignancy in RS, increasing the upgrade rate by10 times. In that study the presence

of calcifications tripled the upgrade rate, while each unit increase in the number of cores reduced the risk by 0.8.

A prior review of RS included an analysis of 20 excision studies [21], finding an overall upgrade rate of 10.4%; 7.5% for those without atypia and 26% in RS with atypia.

A threshold for an acceptable level of risk has not been explicitly agreed upon in this field, but the precedent of BIRADs category 3 lesions, as used in the American College of Radiology, exists. For BIRADs category 3 lesions, the risk of malignancy is likely to be less than 2% and short-term (6 months) imaging surveillance is the accepted management recommendation. Applying this standard, RS without atypia assessed by VABs have a sufficiently low upgrade rate to be considered for short term surveillance, rather than surgery, however the 95% confidence interval for the pooled estimate of 1% upgrade rate was 0–4%. The fact that the upgrades in this group were to DCIS rather than to invasive cancer may provide a further impetus to a non-surgical approach. The 2% (95% CI 1,4%) estimated upgrade rate for RS without atypia, assessed by cores of 8-16G suggests this group may also be considered for non-surgical management. There is an overlap between this group and RS assessed by VABs. We note the upgrade rate for RS without atypia assessed by 14G NCB was 5% (95% CI 3,8%), suggesting that the lower upgrade rate in the 8-16G mixed modality group is attributable to the inclusion of cases assessed by larger caliber biopsies. In predicting the risk of an upgrade, when specific data about the biopsy modality, needle gauge and atypia are available, figures for the relevant specific subgroup should be used, reserving the heterogeneous 8-16G category for situations when the specific parameters cannot be ascertained.

While the small number of reported series precludes meta-analysis and requires caution, a non-surgical approach may also be considered for lesions in three other small special case scenarios. These included RS of ≤ 5 mm without atypia, mammographically occult but sonographically detected RS without atypia and incidental/microscopic RS without atypia. Despite the small number of reports addressing these subgroups, prior estimates indicate that up to 30.2% of all RS found on NCB are incidental to the lesion being targeted [7]. A non-surgical approach for these lesions is likely to have a significant impact in reducing benign open biopsy rates.

The upgrade rates for all other planned subgroups were $\geq 5\%$. We do not espouse any arbitrary risk threshold for avoiding surgery, but using this meta-analysis as a decision aid, the likelihood of concurrent malignant change in each specific clinical context can be predicted and the options and risks discussed with the patient. If observation is chosen, the need for continued, long term imaging surveillance should be emphasized.

In recognising the value of VABs, some centres have suggested a repeat biopsy with a vacuum-assisted device, when high-risk borderline lesions such as RS, are identified on 14G NCB [28, 32]. In the UK screening Program, a creative solution has been implemented that replaces surgery with VAB excision, whereby lesions biopsied previously and found to be RS are re-booked for VAB excision [26]. Since the likelihood of malignancy is low, particularly in the absence of atypia in the initial biopsy, there are no oncologic objections to the piecemeal removal of such lesions and the experience to date has been reassuring. Our meta-analysis included 57 such lesions in 3 series, with no malignant upgrades.

Widening the VAB excision approach to RS with atypia may be more problematic. Such lesions are more likely to harbour undetected foci of DCIS and invasive cancer and the morcellation of cancers by VABs may compromise the histologic evaluation of tumour size and peritumoural lymphovascular invasion. Surgery would still be required for the evaluation of surgical margins.

Despite the general high negative predictive value of MRIs, we note the upgrade rate for MRI guided biopsies of RS was 24% (95% CI 11, 39%), similar to the upgrade rates of unselected series of RS.

The limitations of this study include the absence of information on radiology pathology (R-P) concordance and incomplete data on the number of cores retrieved or the proportion of the lesion left behind. In addition, patient level information regarding age, lesion size, symptoms or findings on clinical breast examination are unavailable. Each of these parameters has been highlighted previously in small studies as possible predictors of upgrade [1, 14, 31]. In a meta-analysis we are restricted by the information reported in eligible studies and the above data are not reported commonly. However, we posit that the biopsy modality may be a surrogate for the extent of sampling, as are the number of cores and the proportion of lesion left behind. We have attempted to present some information regarding the number of cores when available and have highlighted studies from population-based screening services, as distinct from other groups. R-P concordance has been emphasized as a way of enhancing diagnostic accuracy, one recent series finding an upgrade rate of only 2% in concordant cases [8]. We cannot vouch that R-P concordance has been achieved on all studies included, but note the increasing recognition of this factor, particularly in recent series.

The estimates for upgrades in this analysis have been based on excised RS. It is possible that the RS recommended for excision may have significantly different, potentially more worrisome features from those allocated to observation. We have no way of ascertaining if this is the case, but if true, this selection bias would exaggerate our estimates of upgrade rates in RS.

Finally, unlike the present analysis, some groups have included various atypical epithelial proliferations in their upgrade rates [17], finding non-malignant atypia in over 20% of excised RS. The reasoning for the inclusion of non-malignant atypia in upgrade rates is that long term follow up studies of women with RS indicate that the slightly increased risk of subsequent cancer is predicated on the nature of the coexisting proliferative disease [4, 30] and the specific type of the proliferative disease may impact clinical care, including chemoprevention. However, since the focus of the present analysis is on reducing non-malignant surgical biopsies, our estimates of upgrades relate specifically to invasive cancer and DCIS.

Conclusions

Upgrade rates for RS are predictable on the basis of the presence of atypia and core biopsy gauge. RS without atypia assessed by 8-11G VABs has an upgrade rate of only 1% (95% CI 0, 4%) and only to DCIS. Imaging surveillance may be a reasonable option for these patients. The upgrade rates for the other planned RS subgroups ranged between 2%-28%, but can be reduced by VAB excisions, as an alternative to surgery. The estimates from this meta-analysis can inform clinical care.

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Compliance with ethical standards

Conflict of interest Gelareh Farshid and Elizabeth Buckley declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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