

Japanese Journal of Radiology

Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnosis by conventional and contrast enhanced US findings

--Manuscript Draft--

Manuscript Number:	RMED-D-16-00154R2
Full Title:	Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnosis by conventional and contrast enhanced US findings
Article Type:	Original Article
Keywords:	Contrast-enhanced ultrasound; homogeneously enhancing lesion; differential diagnosis
Corresponding Author:	Kengo Yoshimitsu, M.D. Faculty of Medicine, Fukuoka University Fukuoka, JAPAN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Faculty of Medicine, Fukuoka University
Corresponding Author's Secondary Institution:	
First Author:	Ritsuko Fujimitsu
First Author Secondary Information:	
Order of Authors:	Ritsuko Fujimitsu Mikiko Shimakura Hiroshi Urakawa Ayako Morita Yoshinobu Shinagawa, Ph.D. Keiko Sakamoto, Ph.D. Kengo Yoshimitsu, M.D.
Order of Authors Secondary	
Funding Information:	
Abstract:	<p>Objective: To clarify the details of homogeneously enhancing lesions on contrast-enhanced ultrasonography (CEUS) and also to elucidate whether their differential diagnosis is possible.</p> <p>Methods: 73 homogeneously enhancing lesions on CEUS were retrospectively selected. Two radiologists first assessed conventional US findings alone in consensus to differentiate malignant vs benign lesions. Then, qualitative and quantitative CEUS findings were analyzed to determine the useful findings for differential diagnosis. Determined CEUS findings were applied to the indeterminate lesions based on conventional US findings to see whether CEUS may improve the diagnostic performance.</p> <p>Results: There were 42 cancers (58%) out of 73. Sensitivity and specificity using conventional US findings alone were 91% and 55%, respectively. Among the CEUS findings tested, multivariate analysis revealed only the type 3 enhancement pattern, which indicates larger enhancing area than the precontrast hypoechoic lesion, was related to malignancy ($p < 0.05$). By adding this information, however, no improvement was achieved in the diagnostic performance as determined by conventional US findings.</p> <p>Conclusions: Approximately half of the homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulous assessment of the conventional US findings, rather than CEUS findings.</p>

Author Comments:

April 13, 2016

Editorials Board
Japanese Journal of Radiology

Subject: Manuscript, " Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnoses ", Ritsuko Fujimitsu, et al

Gentlemen:

Enclosed are the re-revised version of the above manuscript, with a complete set of figures, which we hereby submit for possible publication in Japanese Journal of Radiology as an original research.

We greatly thank the assistant editor for his or hers invaluable suggestions to our manuscript. We made corrections as suggested by the assistant editor's comments to improve our manuscript. We hope our revision is sufficient for final acceptance in Japanese Journal of Radiology.

Thank you for your consideration.

Sincerely,

Kengo Yoshimitsu, M.D., Ph.D.
Department of Radiology
Faculty of Medicine,
Fukuoka University
7-45-1, Nanakuma, Jonan-ku, Fukuoka, JAPAN, 814-0180
(Fax) 92-801-1011
(Phone)92-864-6652
(e-mail) kengo@fukuoka-u.ac.jp

Homogeneously enhancing breast lesions on contrast enhanced US:
differential diagnosis by conventional and contrast enhanced US findings

Ritsuko Fujimitsu, M.D.

Mikiko Shimakura, M.D.

Hiroshi Urakawa, M.D.

Ayako Morita, M.D.

Yoshinobu Shinagawa, M.D.

Keiko Sakamoto, M.D.

Kengo Yoshimitsu, M.D.

Dept. of Radiology, Faculty of Medicine, Fukuoka University,

7-45-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan

Phone: 81-92-801-1011, Fax:81-92-864-6652

Corresponding author: K Yoshimitsu kengo@fukuoka-u.ac.jp

Authors have no conflicts of interest to declare.

Type of manuscript: original article

Abstract

Objective: To clarify the details of homogenously enhancing lesions on contrast-enhanced ultrasonography (CEUS) and also to elucidate whether their differential diagnosis is possible.

Methods: 73 homogenously enhancing lesions on CEUS were retrospectively selected. Two radiologists first assessed conventional US findings alone in consensus to differentiate malignant vs benign lesions. Then, qualitative and quantitative CEUS findings were analyzed to determine the useful findings for differential diagnosis. Determined CEUS findings were applied to the indeterminate lesions based on conventional US findings to see whether CEUS may improve the diagnostic performance.

Results: There were 42 cancers (58%) out of 73. Sensitivity and specificity using conventional US findings alone were 91% and 55%, respectively. Among the CEUS findings tested, multivariate analysis revealed only the type 3 enhancement pattern, which indicates larger enhancing area than the precontrast hypoechoic lesion, was related to malignancy ($p < 0.05$). By adding this information, however, no improvement was achieved in the diagnostic performance as determined by conventional US findings.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62

Conclusions: Approximately half of the homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulous assessment of the conventional US findings, rather than CEUS findings.

Key words

Contrast-enhanced ultrasound; homogeneously enhancing lesion; differential diagnosis

INTRODUCTION

With the advent of contrast agent for ultrasonography, several researchers have applied this technique, namely contrast enhanced ultrasonography (CEUS), to breast imaging, and not a few promising data have been published in terms of malignancy vs benignity differentiation [1-4]. Generally, it has been reported that irregularly or peripherally enhancing lesions are malignant, whereas homogeneously enhancing ones are benign [1-3]. However, we encounter considerable number of “exceptional” cases in daily practice, which are against the above mentioned rules, particularly for the latter [4-6]. To our knowledge, little has been investigated specifically focused on the differential diagnosis of homogeneously enhancing lesions on CEUS.

This study was conducted, therefore, to clarify the clinico-pathological details of “homogeneously enhancing lesion” on CEUS, and to elucidate whether differentiation between malignant and benign lesions in this particular cohort is possible.

MATERIALS AND METHODS

Between October 2012 and August 2015, 134 patients with 161 suspected breast lesions underwent CEUS in our institute. Among these, the lesions which showed homogeneous enhancement at their peaks, and also for whom final pathological diagnoses were obtained, were retrospectively recruited. In our institute, CEUS is routinely performed as a presurgical procedure, or for patients whose diagnosis is indeterminate or questionable based on conventional radiological workup. Our institutional review board waived obtaining informed consent because of its retrospective nature.

CEUS was performed with a clinical ultrasound unit (LOGIQ E9, GE HealthCare, Milwaukee, WI). Conventional and contrast-enhanced US images were obtained with a ML 6-15MHz and a SL 9MHz linear probes, respectively. Mechanical index was set at 0.2-0.21. After confirming that the target lesions were well visualized at the center of field-of-views, bolus injection of contrast medium (Sonazoid, Daiichi Sankyo, Tokyo, Japan) of 0.015 mL/kg was performed from the antecubital vein, followed by 10mL saline flush. The target lesions were then continuously observed for 90s using real-time grayscale harmonic imaging, the whole process of which was video-

1
2
3 recorded.

4
5
6 All sonographic images and videos were reviewed by two experienced
7
8
9 radiologists (RF and MS) who were experienced in breast sonographic
10
11
12 imaging and blinded to the pathological results. First, the conventional US
13
14
15 images alone were evaluated, and the confidence level of diagnosing malignancy
16
17
18 was determined using 5-point scale in consensus, with scores 1, 2, 3, 4, and 5
19
20
21 indicating definitely benign, possibly benign, indeterminate, possibly
22
23
24 malignant, and definitely malignant, respectively, according to the previously
25
26
27 reported criteria, namely, Breast Imaging Reporting and Data System (BI-
28
29
30 RADS) 2013 [7] for mass lesions and those defined by Ko et al. [8] for non-
31
32
33 mass-like lesions. As for mass lesions, the final score of a certain patient was
34
35
36 determined based on the total balance of the assessment for each finding of
37
38
39 BI-RADS 2013 (Table 1); more specifically, the all findings listed in Table 1
40
41
42 were checked for each lesion, and if findings favoring malignancy or benignity
43
44
45 were dominant, scores 4-5 or 1-2 were given, respectively; if these were
46
47
48 similar in number, score 3 was given. As for non-mass lesions, types Ib and
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

1
2
3 malignancy, respectively, and sensitivity and specificity were calculated.
4

5
6 Then, the enhancement patterns of the lesions on CEUS were reviewed and
7
8
9 divided into the following three groups; type1, in which the degree of
10
11
12 enhancement of the lesions was almost equal to the surrounding breast tissue,
13
14
15 type 2, where the degree of enhancement was greater than that of
16
17
18 surrounding tissue with the area of enhancement being approximately the
19
20
21 same as the precontrast hypoechoic lesion in size, and type 3, in which the
22
23
24 degree of enhancement was greater than that of surrounding tissue, and the
25
26
27 area of enhancement was larger than the hypoechoic lesion on the precontrast
28
29
30 images. On the dynamic phase of contrast enhancement, one radiologist
31
32
33 (RF) manually placed region-of-interest to cover the whole lesion as visualized
34
35
36 on the initial images before contrast arrival, and time-intensity-curve (TIC)
37
38
39 was created, and following indices were semi-automatically calculated: A_{xk}
40
41
42 value was defined as the slope of the tangent at the beginning of TIC
43
44
45 ; time to peak (TTP) was defined as the time period in sec between the
46
47
48 beginning point to the peak of TIC: ascending slope (AS) was defined as the
49
50
51 slope between the beginning point to the peak of TIC.
52
53
54

55
56
57 The correlation between these CEUS parameters (enhancement patterns,
58
59
60
61
62

1
2
3 Axk, TTP, and AS) and malignity vs benignity were assessed and significant
4
5
6 factors for differentiation were sought. Significant factors, if present, were
7
8
9 applied to the above mentioned score 3 groups, namely indeterminate lesions
10
11
12 when assessed solely with conventional US image findings, and sensitivity
13
14
15 and specificity were again calculated to check whether adding CEUS
16
17
18 information might improve the diagnostic capability.
19

20
21
22 For statistical analyses, Wilcoxon Kruskal-Wallis test, Fisher's exact
23
24
25 probability test, and χ^2 test, were used for univariate analyses, and logistic
26
27
28 regression test was used for multivariate analysis. P values of less than 0.05
29
30
31 were considered significant. The statistical software used was JMP version
32
33
34
35 11 (SAS corporation, Cary, USA).
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62

RESULTS

There were 73 patients with 73 lesions with age ranging from 34 to 80 years old (mean 53.2), including 10 fibroadenoma/phyllodes tumors, 12 intraductal papillomas, 19 ductal adenocarcinoma in situ (DCIS), 23 invasive ductal adenocarcinomas (IDC), and 9 other non-specific benign lesions (NSBL). Namely, 58% (42/73) of homogeneously enhancing lesions were malignant in our patient population. All NSBL showed fibrocystic change or adenosis with or without slight inflammatory cell infiltration. The lesions size ranged from 4 to 85 mm in their maximum dimension, with malignant lesions (19.5 ± 15.1 mm) being larger than benign ones (10.5 ± 6.3 mm). Among these, histological diagnoses were made by surgical resection, percutaneous needle biopsy, and cytology for 50, 19, and 4 lesions, respectively.

Diagnosis solely based on conventional US findings

As for mass lesions, two, one, 12, 27, and 7 lesions were given score 1, 2, 3, 4, and 5, respectively; as for non-mass lesions, there were 0, 0, 6, 10, and 8. In total, two, one, 18, 37, and 15 lesions were graded as score 1, 2, 3, 4, and 5, respectively by the two reviewers. The three lesions given scores 1 or 2 were

1
2
3 all benign, and 15 lesions given scores 5 were all malignant. Those scored
4
5
6 as 3 (indeterminate lesions) included 14 benign and 4 malignant lesions.
7
8
9 Those scored as 4 (probably malignant) included 14 benign and 23 malignant
10
11
12 lesions. Thus, when scores 4 and 5 were considered to suggest malignity,
13
14
15 sensitivity, specificity, and accuracy were 90.5% (38/42), 54.8% (17/31), and
16
17
18 75.3% (55/73), respectively.
19
20
21
22
23
24

25 CEUS findings

26
27
28 The details of the CEUS findings vs histological classification are shown
29
30
31 in Table 2. When histology was simply divided into benign vs malignant,
32
33
34 enhancement pattern was the only significant factor, suggesting type 3
35
36
37 enhancement pattern was significantly related to malignancy. When each
38
39
40 disease entity was separately considered, univariate analysis suggested
41
42
43 enhancement pattern and Axk were significant factors, with type 3
44
45
46 enhancement pattern being associated with IDC, and Axk of NSBL being
47
48
49 smaller than those of IP (Table 1). No other indices were significantly
50
51
52 different among the disease entities. Multivariate analysis revealed that only
53
54
55 enhancement pattern was independently significant with the likelihood ratio
56
57
58
59
60
61
62

1
2
3 χ^2 (Chi-square) values of 13.1.
4
5
6
7
8
9

10 **Diagnosis using both conventional US and CEUS findings**
11

12
13 The significant parameter in CEUS finding, namely enhancement pattern,
14
15 was attempted to be incorporated into the diagnosis using conventional US
16
17 findings, however, all 8 lesions showing type 3 enhancement pattern had
18
19 already been diagnosed as malignant by conventional US findings (two and
20
21 six lesions were scored as 5 and 4, respectively). Thus, incorporating CEUS
22
23 finding into conventional US findings did not improve diagnostic performance
24
25 in terms of malignant vs benign differentiation.
26
27
28
29
30
31
32

33
34
35 Representative cases are shown in Fig.s 1-3.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62

DISCUSSION

Our results suggested homogeneously enhancing lesions are not necessarily benign, but considerable number of malignancy (approximately 60% in our cohort) can be included in this group of lesions. Among these, approximately 75% of lesions can be correctly diagnosed as benign or malignant by conventional US findings alone, but one quarter of them (18/73) remain indeterminate.

As for CEUS findings, our factor analysis revealed enhancement pattern and Axk values were significantly related to the final diagnoses of the lesions.

Actually, all 8 lesions showing type 3 enhancement pattern (the degree of enhancement was greater than that of surrounding tissue, and the area of enhancement was larger than the hypoechoic lesion on the precontrast images) were IDC. Histopathological correlation revealed two of these lesions showed strong lymphocytic infiltration around the marginal areas of the lesions (Fig.3). Similar observation, namely peritumoral enhancement around IDC, has already been reported, which have been attributed to DCIS component around IDC, adenosis with lobular hyperplasia or inflammatory cell infiltration around IDC [5, 9-10]. A “crab-craw like microvascular

1
2
3 architecture” or increased microvessel density or vascular endothelial growth
4
5
6 factor expression may be related to this findings [5, 10-12].
7

8
9
10 In contrast to the previous report [1, 6, 9], quantitative indices derived from
11
12 TIC did not serve to the differential diagnosis, except for Axk values, which
13
14 were useful only in differentiating NSBL from IP. NSBL and IP tended to
15
16 show lower and higher Axk values, respectively, among the disease entities
17
18 included in this study. NSBL in our population consisted of fibrocystic
19
20 change or adenosis with or without slight inflammatory cell infiltration,
21
22 possibly representing mastopathy or chronic mastitis. We presume
23
24 angiogenic features may be similar regardless of it benignity or malignity in
25
26 this particular cohort. In addition, multivariate analysis revealed that only
27
28 enhancement pattern, not Axk, was the independently significant factor in
29
30 the differential diagnosis.
31
32
33
34
35
36
37
38
39
40
41

42
43
44 Adding the significant factor derived from CEUS, namely enhancement
45
46 pattern, however, did not improve diagnostic performance solely based on
47
48 conventional US findings. All lesions showing type 3 enhancement pattern
49
50 had readily been diagnosed as malignant, using conventional US findings
51
52
53
54
55
56
57 (Table 1). Thus, CEUS findings, either qualitative or quantitative, added little
58
59
60
61
62

1
2
3 to the differential diagnosis of homogeneously enhancing lesions on CEUS.

4
5
6 We therefore recommend looking back the conventional US findings
7
8
9 meticulously when dealing with the lesions in this particular cohort.

10
11
12 There are several limitations in this study, in addition to the retrospective
13
14
15 nature. First, although the total number of subjects were over 70, both benign
16
17
18 and malignant lesions included various entities of limited number, and
19
20
21 therefore our result may not be applicable to different cohort of different
22
23
24 disease configuration. Ideally, our results should have been tested in another
25
26
27 cohort consisting of homogeneously enhancing lesions. Second, because the
28
29
30 enhancement pattern of the lesions was assessed as compared to that of the
31
32
33 background breast tissue, the results would be affected by the condition of the
34
35
36 background tissue, for example menstrual cycle or age-related fatty change,
37
38
39 in addition to that of the lesions themselves. Third, placement of ROI to
40
41
42 create TIC and subsequent quantitative indices measurement was performed
43
44
45 by one radiologist, which may have caused some bias in the results. Fourth,
46
47
48 qualitative assessment was made by two radiologists in consensus, not by
49
50
51 independent interpretation, which also may have resulted in some bias.
52
53
54 Further prospective study with larger population and meticulous design
55
56
57
58
59
60
61
62

1
2
3 would be needed to solve these problems.

4
5
6 In conclusion, radiologists should be aware that almost half of
7
8
9
10 homogeneously enhancing lesions on CEUS are malignant, and
11
12
13 differentiation of malignant from benign lesions may be possible, at least to
14
15
16 some extent, by meticulously referring to the conventional US findings, not
17
18
19 to CEUS findings.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62

References

1. Zhao H, Xu R, Ouyang Q, Chen L, Dong B, Huihua Y, Contrast-enhanced ultrasound is helpful in the differentiation of malignant and benign breast lesions. *Euro J Radio*. 2010; 73: 288-293
2. Du J, Wang L, Wan CF, Hua J, Fang H, Chen J, Li FH. Differentiating benign from malignant solid breast lesions: Combined utility of conventional ultrasound and contrast enhanced ultrasound in comparison with magnetic resonance imaging. *Eur J Radiol* 2012; 33: 3890–3899.
3. Miyamoto Y, Ito T, Takada E, Omoto K, Hirai T, Moriyasu F. Efficacy of Sonazoid (Perflubutane) for contrast-enhanced ultrasound in the differentiation of focal breast lesions: Phase 3 multicenter clinical trial. *AJR* 2014; 202: W400-407
4. H.Liu, YX Jiang, JB Liu, et al. Evaluation of breast lesions with contrast-enhanced ultrasound using the microvascular imaging technique: Initial observations. *The Breast* 2008; 17: 532-539
5. H.Liu, YX.Jiang, JB Liu, et al. Contrast-enhanced breast ultrasonography Imaging features with histopathologic correlation. *J Ultrasound Med*. 2009; 28: 911-920
6. Wan CF, Du J, Fang H, et al. Evaluation of breast lesions by contrast enhanced ultrasound: Qualitative and quantitative analysis. *Euro J Radio* 2012;81:e444-e450

- 1
2
3 7. American College of Radiology. BI-RADS® – Ultrasound 2013.
4
5
6 <http://www.acr.org/Quality-Safety/Resources/BIRADS/Ultrasound>
7
- 8
9 8. Ko KH, Hsu HH, Yu JC, et al. Non-mass-like breast lesions at ultrasonography:
10
11 feature analysis and BI-RADS assessment. *EJR* 2015;84:77-85
12
13
- 14
15 9. Jiang YX, Liu H, Liu JB, et al. Breast tumor size assessment: Comparison of
16
17 conventional ultrasound and contrast-enhanced ultrasound. *Ultrasound in Med. &*
18
19 *Biol.* 2007; 33: 1873-1881.
20
21
22
- 23
24 10. Du J, Li FH, Fang H, et al. Microvascular Architecture of Breast Lesions;
25
26
27 Evaluation With Contrast-Enhanced Ultrasonographic Micro Flow Imaging. *J*
28
29 *Ultrasound Med.* 2008; 27: 833-842
30
31
32
- 33
34 11. YJ.Li, G Men, Y Wang, et al. Perfusion heterogeneity in breast tumors for assessment
35
36 of angiogenesis. *J Ultrasound Med.* 2013; 32:1145-1155
37
38
- 39
40 12. Liu H, Jiang YX, Dai Q, et al. Peripheral enhancement of breast cancers on contrast-
41
42 enhanced ultrasound: Correlation with microvessel density and vascular endothelial
43
44 growth factor expression. *Ultrasound in Med. & Biol.*, 2014;40: 293–299
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62

Table 1 Criteria for malignity and benignity of the lesions based on conventional sonographic findings before contrast enhancement

	benign	indeterminate	malignant
Mass lesion [7]*			
shape	Oval	Round	Irregular
orientation	Parallel to the skin		Not parallel to the skin
margin	Circumscribed	Microlobulated	angular, indistinct, spiculated
internal echo	Aechoic, hyperechoic	Isoechoic, hypoechoic	Complex,
posterior acoustic features		Enhancement, None	shadowing, combined
calcification			In mass, intraductal
architectural distortion			yes
Duct change			yes
Non-mass lesion [8]**			
types		type Ia, type IIa, type III, type IV	type Ib, type IIb

* Original reference #7 includes other factors including skin appearances, Doppler or elastography information. However, in our patients, none showed skin thickening, skin retraction, or edema: Doppler sonography and elastography were obtained in limited number of cases. These findings were therefore omitted in the table.

** Type I ductal non-mass-like (NML) pattern: parallel orientation of multiple duct-like structures without calcifications

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

(type Ia) or with associated calcifications (type Ib). Type II nonductal NML pattern: a geographic or mottled area that does not give a discrete mass, and may present without calcifications (type IIa) or with associated calcifications (type IIb). Type III NML pattern: associated with architectural distortion, Type IV NML pattern: associated with posterior acoustic shadowing [8].

Table 2 Correlation between contrast-enhanced US findings and histology

CEUS findings	benign	malignant	P values	Disease entities					P values	
				benign			malignant		Uni	Mul
				FA/Phyl	IP	NSBL	IDC	DCIS		
Ehn.pattern Type 1/2/3	14/17/0	23/11/8	0.004	3/7/0	4/8/0	7/2/0	11/4/8	12/7/0	0.01	0.0005
Axk	6.5 ± 3.2	7.1 ± 3.5	NS	6.8 ± 2.5	8.2 ± 3.3	4.1 ± 2.0	7.4 ± 4.2	6.8 ± 2.6	0.044*	NS
TTP	9.6 ± 3.0	9.7 ± 4.8	NS	9.3 ± 2.2	8.9 ± 1.4	10.1 ± 5.8	10.8 ± 4.6	8.9 ± 4.5	NS	
AS	2.2 ± 0.8	2.2 ± 1.0	NS	2.3 ± 0.7	2.4 ± 0.5	1.9 ± 1.1	2.2 ± 1.1	2.2 ± 0.9	NS	

CEUS: contrast-enhanced ultrasonography, Enh.pattern: enhancement pattern, Axk: the slope of the tangent at the beginning of time-intensity-curve, TTP: time to peak, AS: ascending slope.

FA: fibroadenoma, Phyl: phyllodes tumor, IP: intraductal papilloma, NSBL: non-specific benign lesion, IDC: invasive ductal carcinoma, DCIS: ductal carcinoma in situ, Uni: univariate analysis, Mul: multivariate analysis

※ indicates NSBL vs IP

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure legends

Fig.1 Pathologically proven fibroadenoma in a 65 year-old woman.

1a Conventional sonography revealed an oval shaped, well circumscribed mass of 10 mm in its greatest dimension, with an internal echogenicity similar to that of the adjacent adipose tissue, associated with slight posterior acoustic enhancement (arrows).

1b Contrast-enhanced sonography showed homogeneous enhancement of the lesion, corresponding to type 2 enhancement pattern (arrows). A_{vk} value was semi-automatically calculated to be 3.82 (time-intensity curve not shown).

1c Microscopic appearance of the lesion (hematoxylin and eosin staining, original magnification x100). Arrow indicate the boundary of the lesion.

Fig.2 Ductal carcinoma in situ in a 41 year-old woman.

2a Conventional sonography reveals a well-demarcated hypoechoic lesion without mass formation, measuring 30 mm in its greatest dimension (arrows).

2b Contrast-enhanced sonography showed homogeneous enhancement of the whole lesion, which is indistinguishable from the background tissue, in keeping with type 1 enhancement pattern. A_{vk} value was semi-

1
2
3 automatically calculated to be 8.22 (time-intensity curve not shown).

4
5
6 2c Microscopic appearance of the lesion (hematoxylin and eosin staining,
7
8
9 original magnification x200). Arrow indicate the calcification within the
10
11
12
13 lesion..

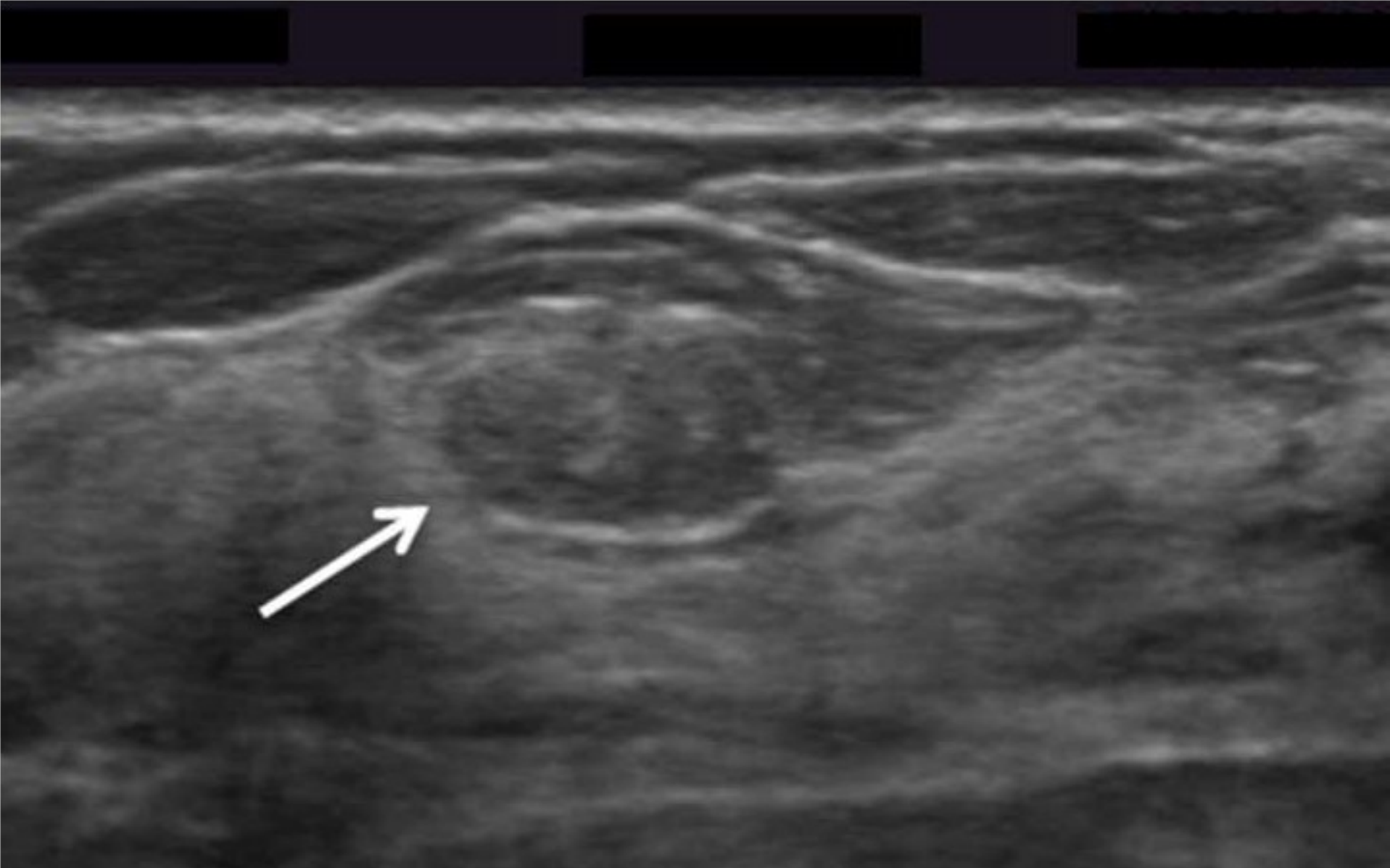
14
15
16
17
18
19 Fig.3 Invasive ductal carcinoma in a 49 year-old woman.

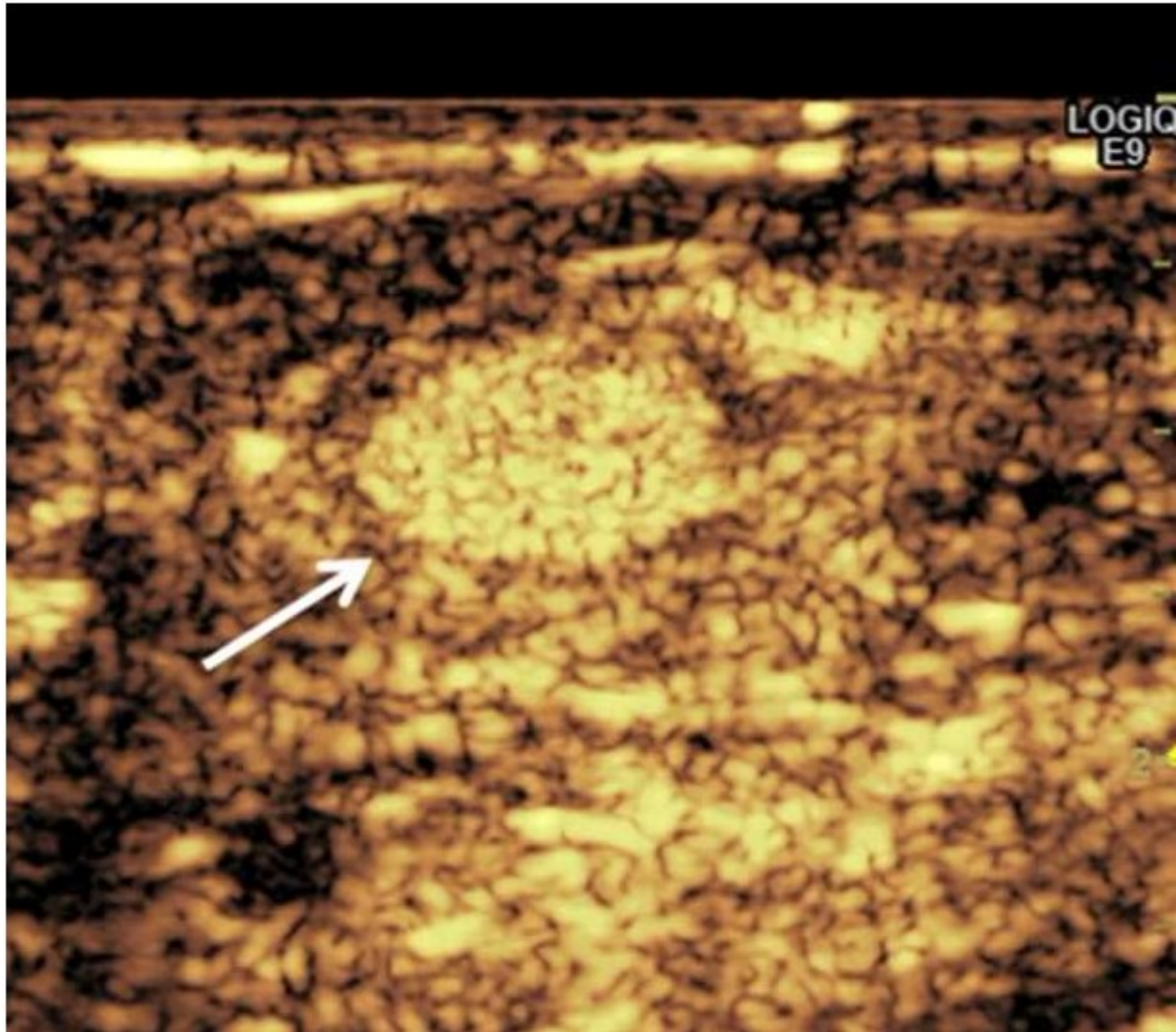
20
21
22 3a Conventional sonography reveals an irregularly shaped hypoechoic
23
24
25 mass of 24 mm in its greatest dimension, showing spiculated margin and
26
27
28 slight posterior shadowing (arrows).

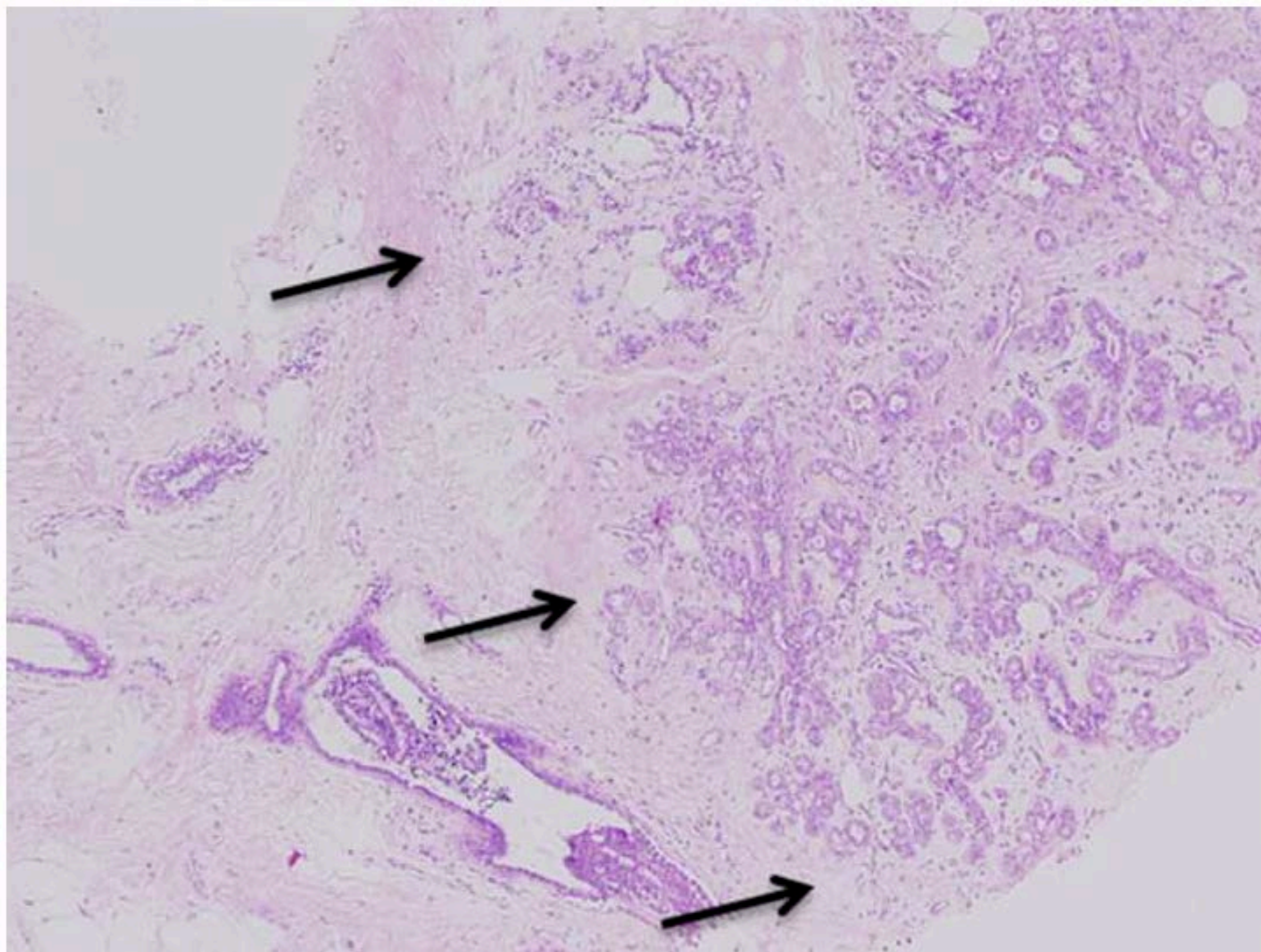
29
30
31
32 3b Contrast-enhanced sonography showed homogeneous enhancement, the
33
34
35 size of which was larger than the hypoechoic area as observed on precontrast
36
37
38 image, in keeping with type 3 enhancement pattern. Axk value was 3.08
39
40
41 (time-intensity curve not shown)

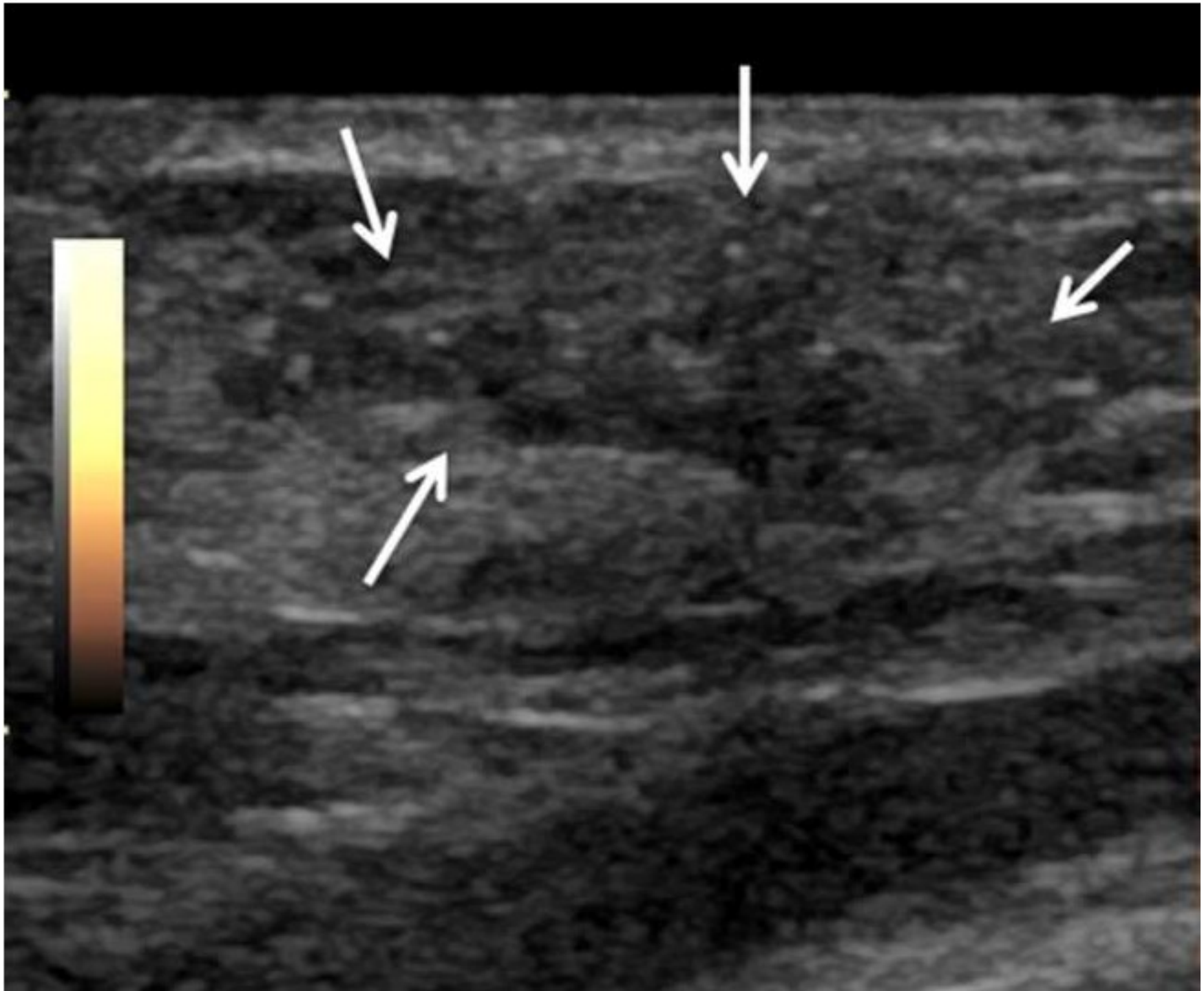
42
43
44 3c Pathological specimen reveals prominent lymphocytic infiltration
45
46
47 (arrows) around the margin of the lesion (C), which may explain the extensive
48
49
50 peritumoral enhancement (hematoxylin and eosin stain, original
51
52
53 magnification x 200).
54
55
56
57
58
59
60
61
62
63
64
65

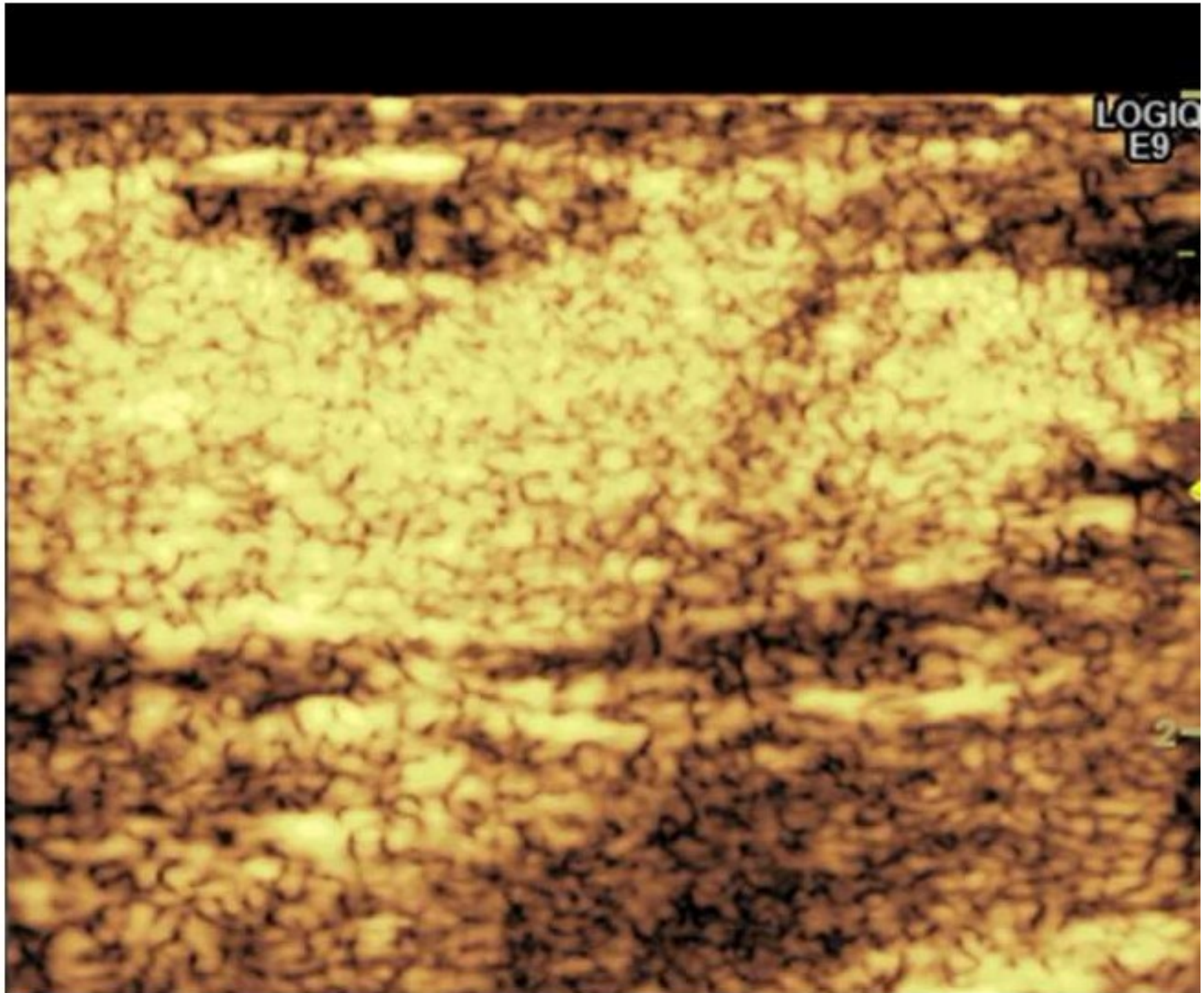
Figure

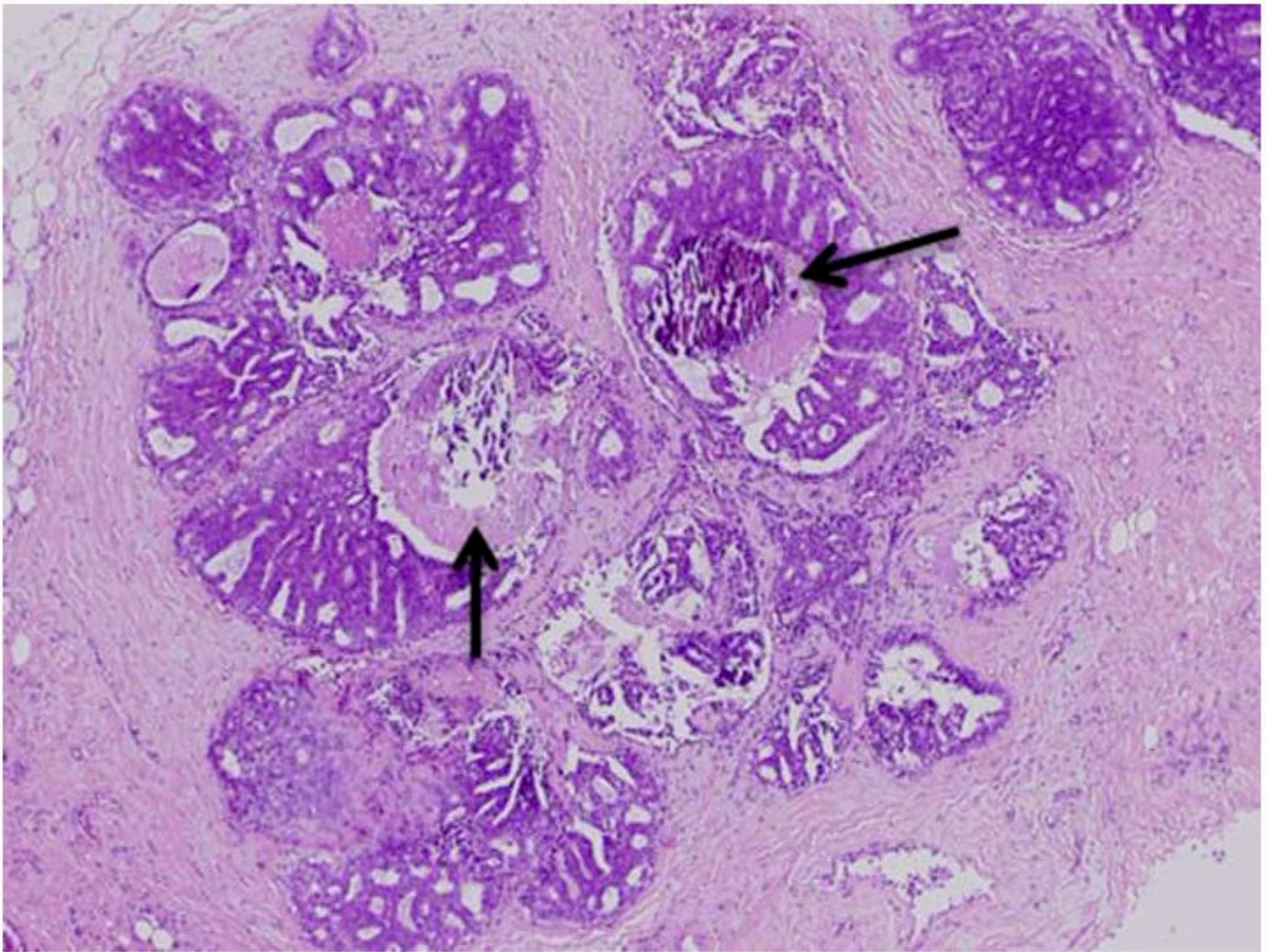


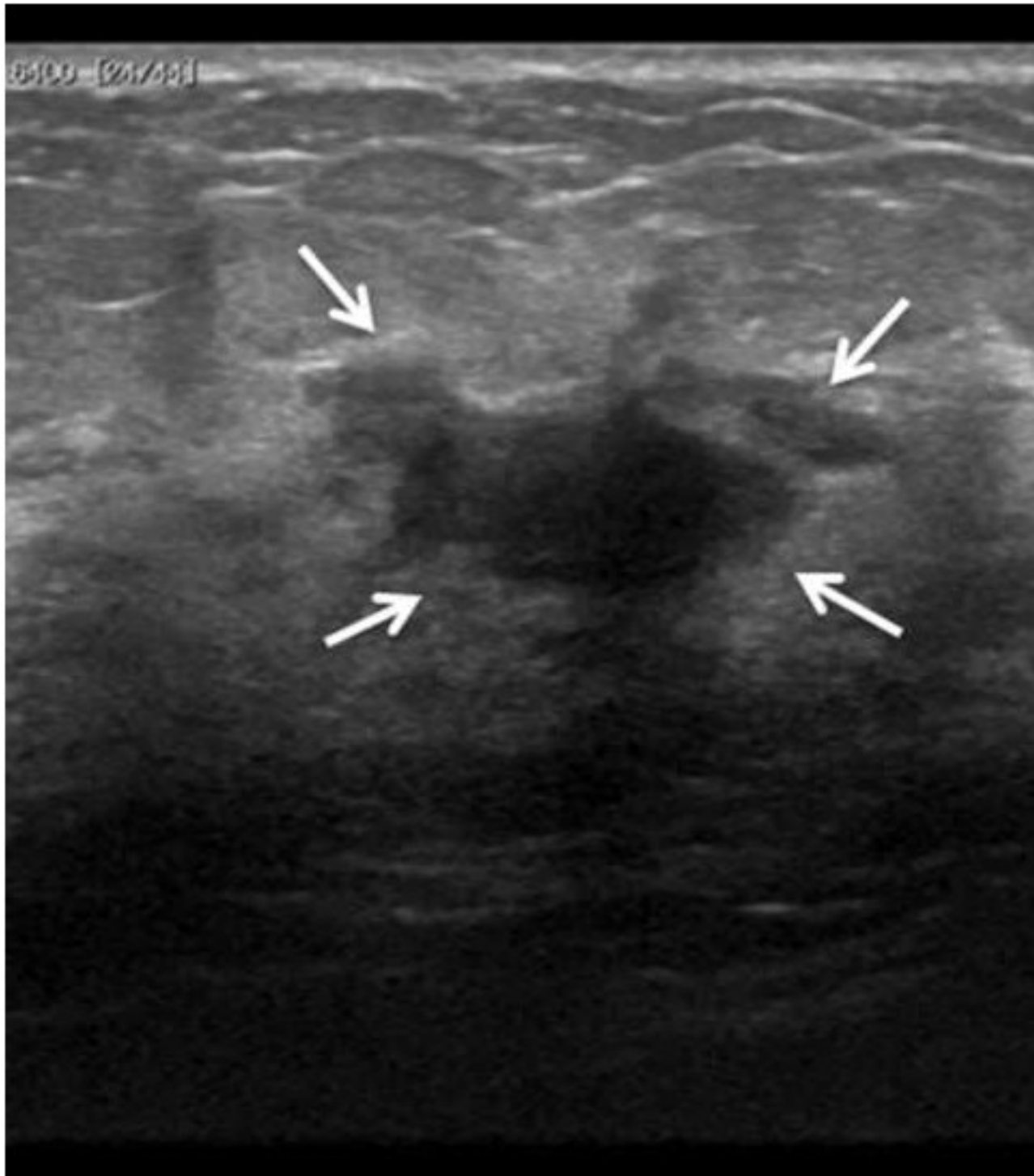


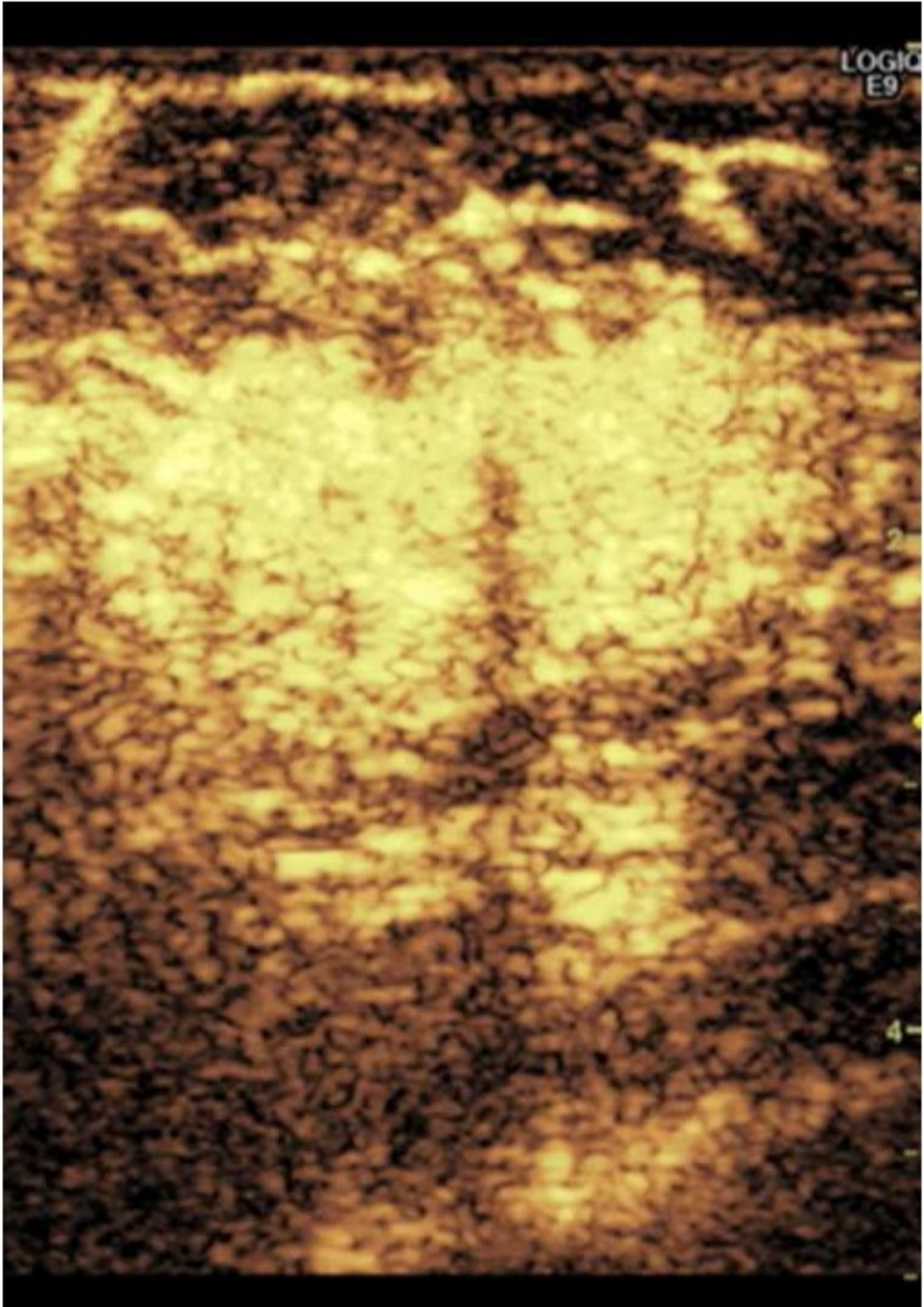


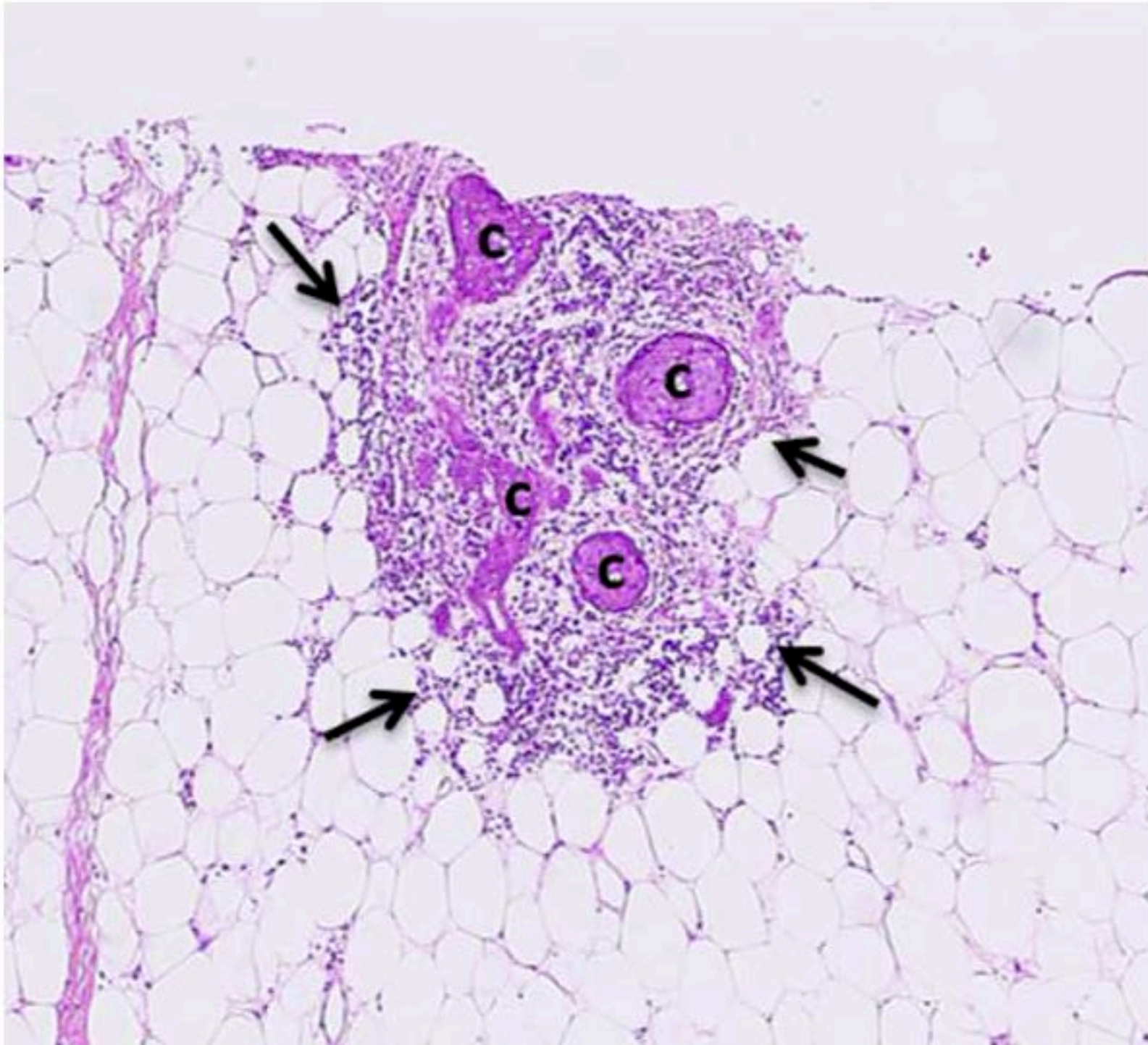












Acknowledgement

Authors greatly thank Professor Kazuki Nabeshima, Department of Pathology, Faculty of Medicine, Fukuoka University, for providing pathological data, and Professor Akinori Iwasaki, Department of Thoracic, Endocrine and Pediatric Surgery, Faculty of Medicine, Fukuoka University, for providing patients' clinical information.