Eur J Cancer Clin Oncol, Vol. 20, No. 6, pp. 765–770, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Prognostic Significance of Residual Cancer Tissue after Diagnostic Biopsy in Breast Carcinoma. Three-year Short-term Results*

JOHAN A. ANDERSEN, MOGENS BLICHERT-TOFT,† JOHAN KJÆRGAARD, KNUD W. ANDERSEN and HENNING T. MOURIDSEN

The Danish Breast Cancer Cooperative Group (DBCG), Finsen Institute, 2100 Copenhagen Ø, Denmark

Abstract—*Among 3264 cases of breast carcinoma undergoing diagnostic biopsy and frozen section followed by one-stage mastectomy, the occurrence of residual cancer tissue (RCT) was evaluated as part of a prospective, nationwide trial in Denmark. RCT was defined by the presence of cancer left in relation to the biopsy cavity in the mastectomy specimen. A significantly higher cumulative recurrence rate within 3 yr was found in cases with residual cancer compared to cases without this finding. The difference was most pronounced in the premenopausal high-risk group. Therefore, RCT in the wall of the biopsy cavity is considered a prognostic hazard by itself.*

INTRODUCTION

THE QUESTION of whether or not biopsy of a breast carcinoma interferes with the prognosis has been seriously discussed during the last 50 yr. Although it is generally agreed today that indeterminate lesions of the breast should be removed by biopsy for diagnostic purposes, the biopsy procedure is still being debated. Especially, it is questioned whether excisional biopsy rather than incisional biopsy should be used in order to lessen the possibility of tumour spread.

Honoured surgeons such as Adair [1, 2], Harrington [3, 4] and Urban [5, 6] have stressed the value of wide excision of the entire tumour. Their statements, albeit undocumented, have made excisional biopsy the general practice throughout the world. Other surgeons, first and foremost Haagensen [7, 8], seem to prefer the principle of incisional biopsy except in the case of very small tumours. Their philosophy is that "carcinoma frequently infiltrates far beyond the grossly visible limits of the disease, and no surgeon can hope that a local excision will get beyond it." Therefore, only a tiny wedge of the tumour is removed for frozen section.

Also, in Denmark wide excision of the entire tumour has been advocated, albeit not practised systematically. The prognostic hazard of this biopsy policy was considered when the first Danish adjuvant trials in primary breast cancer (Danish Breast Cancer Cooperative Group, DBCG) started nationwide in 1977. By historical tradition [9], careful histological investigation of residual cancer tissue (RCT) in the wall of the biopsy cavity was from the start included in this prospective study. Therefore, we may now be able to evaluate whether RCT is of any early prognostic significance.

MATERIALS AND METHODS

The DBCG-77 project and its practical implementation are described in detail elsewhere [10]. More than 90% of all operable primary breast carcinomas in Denmark are included in the trials and of these about 70% enter prospective protocols. Grounds have been given for all exclusions from protocols, and only about 10% of exclusions are due to protocol violations.

Based on histopathological findings, patients are divided into low- and high-risk groups. The low-risk group comprises cases with a tumour 5 cm or less in diameter, without invasion to skin or deep fascia and without metastatic axillary lymph nodes. The high-risk group is defined by a tumour more than 5 cm in diameter, by

Accepted 2 December 1983.
*This work was supported by grants from The Danish Cancer Society and the Danish Medical Research Council.
†To whom correspondence and requests for reprints should be addressed at: Department of Surgery K, Odense University Hospital, DK-5000 Odense, Denmark.

histologically demonstrable invasion to skin or deep fascia or by spread to axillary lymph nodes.

Both low- and high-risk groups are without clinical evidence of distant metastases, as based on physical examination, X-ray of lungs and bone scintigraphy.

The treatment schedule is as follows: surgical procedure is total mastectomy with partial axillary dissection. The low-risk group received no further treatment and a watch policy is followed. The high-risk group, on the other hand, receives postoperative irradiation and the patients are randomly assigned to receive no further therapy (control groups) or to receive a 1-yr adjuvant systemic treatment (Fig. 1).

In this study only patients undergoing biopsy and frozen section followed by one-stage mastectomy are included, thereby excluding patients having delayed mastectomy for various reasons.

RCT is defined by the presence of cancer left in relation to the biopsy cavity in the mastectomy specimen. From our study design it is not possible to evaluate whether RCT is the result of incisional biopsy or intended excisional biopsy which has failed, as mentioned earlier. The pathological procedure includes careful macroscopical evaluation of the wall of the biopsy cavity, combined with histological investigation of two or more paraffin-embedded tissue sections.

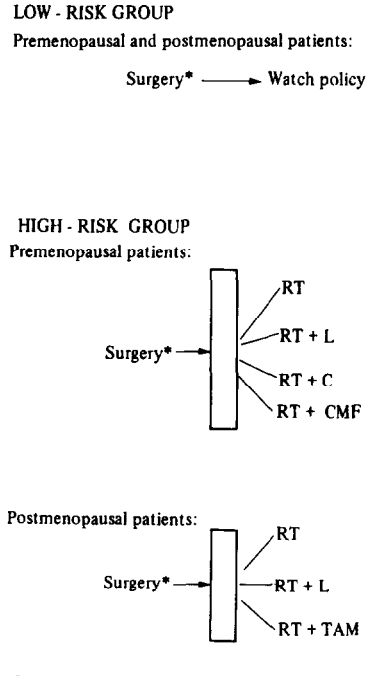

Fig. 1. Study design in the DBCG-77 trials.

'Recurrence' is defined as the first loco-regional recurrence and/or distant metastasis discovered during systematical follow-up, and also cases of deaths, whether or not recurrence was established.

The cumulative recurrence rate as to whether or not RCT has been found is related to risk group, age, adjuvant treatment arms and histological parameters of known prognostic significance, i.e. number of positive axillary lymph nodes, penetration of lymph node capsule, tumour size, anaplasia grading, multicentric carcinoma and invasion to skin, deep fascia, nerves or blood vessels.

The 3-yr recurrence-free survival rates are compared by the stratified log-rank test. In addition, a Cox analysis [11] was performed to identify essential prognostic factors.

RESULTS

As of 1 January 1982, 5077 patients have entered protocols, of whom 3264 fulfill our criteria. The low-risk group comprises 1620 cases, 529 premenopausal and 1091 postmenopausal. The high-risk group includes 1644 cases, 588 premenopausal and 1056 postmenopausal.

The ratio between loco-regional and distant metastases in our study is 1:1 for the low-risk group and 1:9 for the high-risk group. Thus in the premenopausal high-risk group the exact number of recurrences was 120, of which only nine were loco-regional.

In low- and high-risk groups, RCT is found in 33 and 67% respectively.

The overall significance of RCT including all breast cancer cases appears from Fig. 2. A significantly higher cumulative recurrence rate is found in these cases than in cases without RCT.

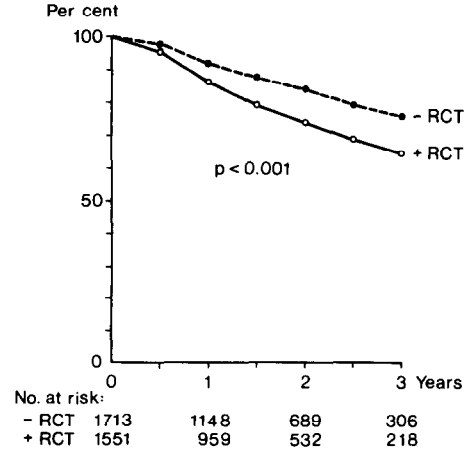

Fig. 2. Overall recurrence-free survival for patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen.

Quite the same trend is obvious when the results are considered separately in the pre- and postmenopausal low- (Fig. 3) and high-risk groups (Fig. 4). However, in these subgroups the difference is significant only in the high-risk group.

The high-risk patients were randomized to different systemic adjuvant therapies or to no further therapy (control groups) (Fig. 1). In all these subgroups a consistently higher recurrence rate was observed in patients with RCT than in patients without RCT (data not shown).

Tables 1–5 present the cumulative recurrence rate in cases with or without RCT in relation to the most essential prognostic patho-anatomical parameters, i.e. number of positive axillary lymph nodes (Table 1), tumour size (Tables 2 and 3) and anaplasia grading (Tables 4 and 5). The premenopausal high-risk group with RCT shows in all these relations a higher cumulative recurrence rate than the group without RCT (Tables 1, 3 and 5). As regards the postmenopausal high-risk group, similar trends are observed but in most relations the differences are not significant (Tables 1, 3 and 5). In the low-risk group no relationship appears (Tables 2 and 4).

In patients with multicentric cancer, penetration of lymph node capsule, invasion to skin, deep fascia, nerves and blood vessels, the number of cases is insufficient for statistical analysis. However, in most relations patients with RCT have a higher recurrence rate than patients without RCT (data not shown).

The Cox analysis identifies RCT together with the state of lymph nodes, grade of anaplasia and treatment arms as the most essential prognostic factors.

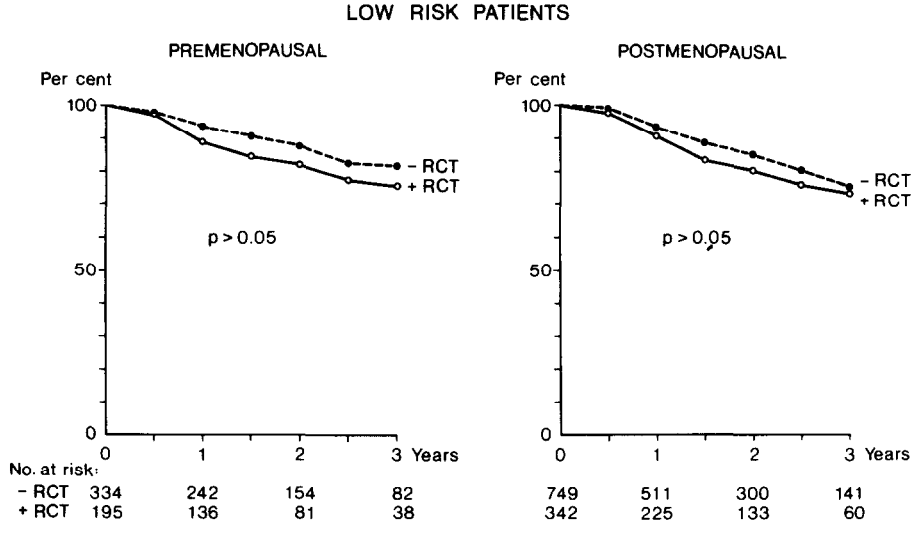

Fig. 3. Recurrence-free survival for low-risk pre- and postmenopausal patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen.

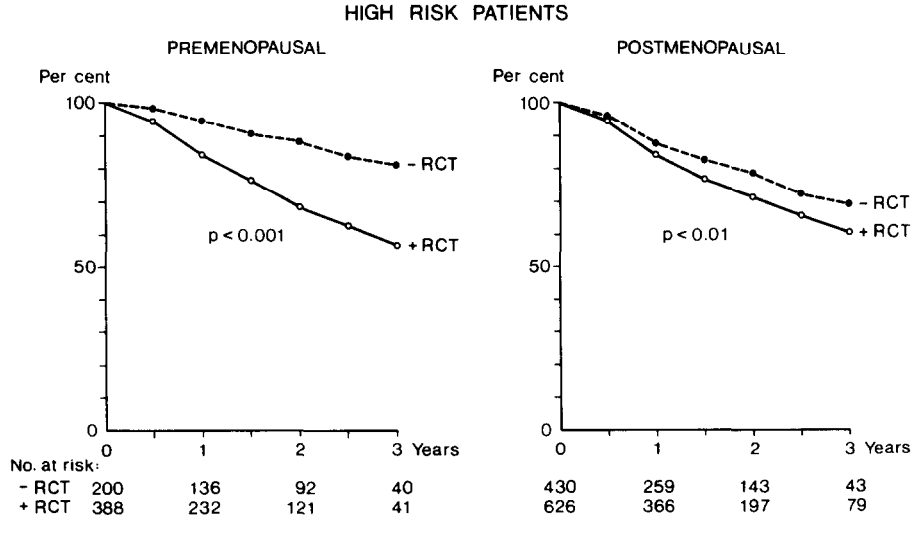

Fig. 4. Recurrence-free survival for high-risk pre- and postmenopausal patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen.

Table 1. Three-year recurrence-free survival rate (RFS), number of patients (n) and significance level (P) for high-risk patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen in relation to the number of positive axillary lymph nodes

No. of positive axillary lymph nodes	High-risk patients									
	Premenopausal					Postmenopausal				
	-RCT		+RCT			-RCT		+RCT		
	RFS (%)	n	RFS (%)	n	P	RFS (%)	n	RFS (%)	n	P
0	86	23	83	82	>0.05	79	51	72	151	>0.05
1–3	81	147	59	176	<0.001	72	296	68	284	>0.05
⩾4	78	30	37	130	<0.05	55	83	41	191	>0.05

Table 2. Three-year recurrence-free survival rate (RFS), number of patients (n) and significance level (P) for low-risk patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen in relation to tumour size

Tumour size (cm)	Low-risk patients									
	Premenopausal					Postmenopausal				
	-RCT		+RCT			-RCT		+RCT		
	RFS (%)	n	RFS (%)	n	P	RFS (%)	n	RFS (%)	n	P
0.0–3.5	83	252	75	131	>0.05	79	563	72	206	>0.05
3.6–5.0	76	79	76	60	>0.05	63	176	76	131	>0.05

Table 3. Three-year recurrence-free survival rate (RFS), number of patients (n) and significance level (P) for high-risk patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen in relation to tumour size

Tumour size (cm)	High-risk patients									
	Premenopausal					Postmenopausal				
	-RCT		+RCT			-RCT		+RCT		
	RFS (%)	n	RFS (%)	n	P	RFS (%)	n	RFS (%)	n	P
0.0–3.5	86	123	65	144	<0.01	73	256	66	198	>0.05
3.6–5.5	77	53	56	129	<0.05	67	120	62	222	>0.05
>5.5	71	23	47	113	>0.05	60	53	51	199	>0.05

Table 4. Three-year recurrence-free survival rate (RFS), number of patients (n) and significance level (P) for low-risk patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen in relation to anaplasia grading

Anaplasia grading	Low-risk patients									
	Premenopausal					Postmenopausal				
	-RCT		+RCT			-RCT		+RCT		
	RFS (%)	n	RFS (%)	n	P	RFS (%)	n	RFS (%)	n	P
I	92	102	84	51	>0.05	81	229	69	102	<0.05
II	74	136	67	75	>0.05	72	310	72	137	>0.05
III	71	40	66	26	>0.05	64	74	70	35	>0.05
None*	85	56	82	43	>0.05	79	136	88	68	>0.05

*Other than ductal carcinomas (NOS).

Table 5. Three-year recurrence-free survival rate (RFS), number of patients (n) and significance level (P) for high-risk patients with primary breast cancer with (+RCT) and without residual cancer tissue (-RCT) in the mastectomy specimen in relation to anaplasia grading

	High-risk patients									
	Premenopausal					Postmenopausal				
Anaplasia grading	-RCT		+RCT			-RCT		+RCT		
	RFS (%)	*n*	RFS (%)	*n*	*P*	RFS (%)	*n*	RFS (%)	*n*	*P*
I	86	53	73	54	>0.05	79	122	77	143	>0.05
II	82	109	51	203	<0.001	69	209	55	321	<0.01
III	76	23	50	76	>0.05	49	63	46	92	>0.05
None*	72	15	65	55	>0.05	82	36	67	70	>0.05

*Other than ductal carcinomas (NOS).

DISCUSSION

In this prospective trial of patients with primary breast carcinoma, we analysed the recurrence rate in patients with and without RCT in the mastectomy specimen.

In the high-risk group, the cumulative recurrence rates within 3 yr were significantly higher in patients with RCT compared to patients without RCT, and similar trends but no significant differences were observed in the low-risk group.

When relating the recurrence rates in patients with and without RCT to other prognostic variables, similar results were achieved within the specific subgroups. It must be stressed, however, that the results are based on up to 3 yr of follow-up only.

There are two immediate explanations to these findings. One is that the presence of RCT virtually reflects the growth pattern and biology of the specific tumour, i.e. the presence of RCT is a specific prognostic factor unrelated to the surgical procedure. The fact that the results were not related to histopathological tumour criteria makes this theory unlikely. More probable is the possibility that cutting through the tumour in itself increases the recurrence rate by some unknown mechanism. In this connection, it should be borne in mind that the RCT is removed from the body by mastectomy within a short time. Therefore, we are dealing with very rapid-acting mechanisms.

The results presented here agree with results previously reported by Pierce *et al.* [12], whose study included 96 patients. In 55 patients who had undergone excisional biopsy, the 5-yr survival rate was 70.9%. In another 41 patients who had undergone incisional biopsy, the 5-yr survival rate was only 47.5%. Unfortunately, neither staging of the disease nor histological grading of malignancy was analyzed in relation to the type of biopsy in question. Furthermore, in all cases the mastectomy was delayed for days or weeks. Therefore it is not possible to compare the results of their series with ours. Nevertheless, there is agreement as to the hazards of RCT in the wall of the biopsy cavity in the two studies.

REFERENCES

1. Adair FE. Clinical manifestations of early cancer of the breast: with a discussion on the subject of biopsy. *N Engl J Med* 1933, **208**, 1250–1255.
2. Adair FE. The role of surgery and irradiation in cancer of the breast. *JAMA* 1943, **121**, 553–559.
3. Harrington SW. Carcinoma of the breast: surgical treatment, and results five, ten, and fifteen years after radical amputation. *Surg Gynecol Obstet* 1933, **56**, 438–441.
4. Harrington SW. Survival rates of radical mastectomy for unilateral and bilateral carcinoma of the breast. *Surgery* 1946, **19**, 154–166.
5. Urban JA. The case against delayed operation for breast cancer. *CA* 1971, **21**, 132–133.
6. Urban JA. Management of operable breast cancer: the surgeon's view. *Cancer* 1978, **42**, 2066–2077.
7. Haagensen CD, Stout AP. Carcinoma of the breast: III. Results of treatment, 1935–1942. *Ann Surg* 1951, **134**, 151–172.
8. Haarensen CD. Incisional biopsy. In: *Diseases of the Breast*, 2nd Ed. Philadelphia, PA, W. B. Saunders, 1971, 143–145.

9. Engelbreth-Holm J. Proeveexcision og metastaserisiko: en oversigt. *Ugeskr Laeger* 1942, **43**, 1105–1109.
10. Andersen KW, Mouridsen HT, Castberg T *et al.* Organisation of the Danish adjuvant trials in breast cancer. *Dan Med Bull* 1981, **28**, 102–106.
11. Cox DR. Regression models and life tables. *J R Statist Soc (B)* 1972, **34**, 187–202.
12. Pierce EH, Clagett OT, McDonald JR *et al.* Biopsy of the breast followed by delayed radical mastectomy. *Surg Gynecol Obstet* 1956, **103**, 559–564.