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The Effect of Supraclavicular Lymph Node Irradiation upon the Thyroid Gland in the Post-operative Breast Carcinoma Patients

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To identify the effect of post-operative irradiation to the thyroid gland in patients with breast carcinoma. Seventy seven patients with partial or total mastectomized breast carcinoma who received routine irradiation therapy (Hockey stick method: supraclavicular, internal mammary lymph nodes, and chest wall irradiation with 5,040 rads, divided into 30 treatments) were reviewed in terms of their ipsilateral thyroid gland response. All patients had the bilateral thyroid sizes measured annually by ultrasonography before and after radiation therapy. In the one-year follow-up group (n=77), 32 patients (41.5%) demonstrated decreased ipsilateral thyroid gland size after Hockey Stick irradiation therapy (p=0.428), in the two-year follow-up group (n=37), 26 patients (70.3%) demonstrated decreased gland size after Hockey Stick irradiation (p=0.001), and in the three-year follow-up group (n=21), 15 patients (71.4%) showed a decreased thyroid gland size (p=0.005). Most the patients with breast carcinoma (32/77 at the one-year follow-up, 26/37 at the two-year follow-up, and 15/21 at the three-year follow-up) after post-operative Hockey Stick irradiation therapy showed reduced ipsilateral thyroid gland size. Routine en face treatment of the supraclavicular lymph nodes, using the Hockey Stick method, should be reconsidered.

Key Words: Breast, carcinoma, radiation, thyroid, supraclavicular lymph node

INTRODUCTION

Radiation therapy has frequently been used to treat breast cancer patients that develop loco-regional tumor recurrence, in the ipsilateral chest wall, axillary region, infraclavicular, supraclavicular fossa or internal mammary lymph nodes, following mastectomy. RT has also been used adjuvantly following mastectomy, particularly in patients who present with locally advanced disease.

Routine post-operative irradiation of breast cancer patients involves the irradiation of the ipsilateral supraclavicular fossa and of the internal mammary lymph nodes with 4,040 - 5,040 rads divided into 30 treatments. This irradiation method is usually called the Hockey Stick method. The Hockey Stick portal treats the internal mammary nodes and the ipsilateral supraclavicular nodes in a single field, as is directly applied to the anterior thorax. This anterior nodal field, which encompasses all regional nodal sites, has traditionally been called the Hockey Stick field because of its shape. Planning CT (Fig. 1) is undertaken prior to

Fig. 1. The planning CT shows that the supraclavicular lymph node irradiation is located at the same axial plane as the thyroid gland. (TH, thyroid gland; SC, supraclavicular lymph node bearing area).

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applying the Hockey Stick method, and should show the supraclavicular lymph node, the internal mammary lymph node, and the chest wall level, it should also should also confirm that the level of the supraclavicular lymph node irradiation is located in the same axial plane as the thyroid gland. The simulation plain film shown in Fig. 2. illustrates the ipsilateral thyroid gland included in the supraclavicular lymph node radiation field, and the medial border of the radiation field of the supraclavicular lymph node at the midline of the Hockey Stick neck. Therefore, the ipsilateral thyroid gland is included in the supraclavicular lymph node radiation field. The diagram of the radiation dose (Fig. 3) applied in Hockey Stick irradiation therapy shows that the area within the red line receives 100% of the applied 5,040 rads. During supraclavicular lymph node irradiation, the ipsilateral thyroid gland is exposed to 100% of the radiation dose, because the superficial skin thickness of the thyroid gland is thin compared with that of other sites, the ipsilateral thyroid gland is expected to receive more radiation (105%) than the ipsilateral supraclavicular lymph node. Measurement of the dimensions of the normal thyroid gland before Hockey Stick irradiation, involves measuring the distance between the medial border of the common carotid artery and the lateral border of the trachea (Fig. 4A). The size of the thyroid gland was found to be considerably reduced at the ipsilateral thyroid gland after 2 years of Hockey Stick irradiation (Fig. 4B).

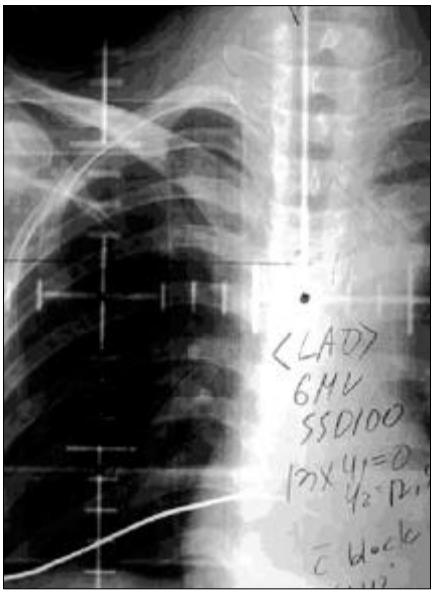


Fig. 2. The simulation plain film showing an ipsilateral thyroid gland included in the supraclavicular lymph node radiation field.

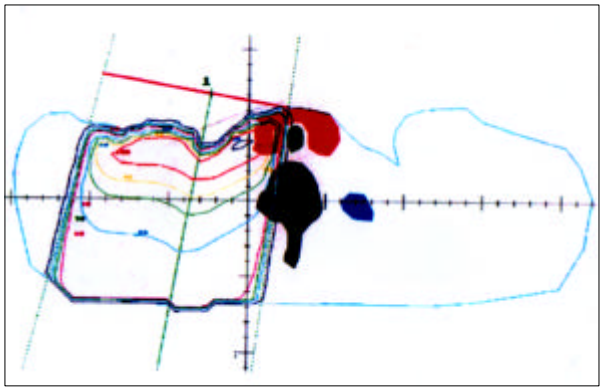


Fig. 3. Diagram of radiation dose by the Hockey Stick method showing the 5,040 rad projected 100% area bounded by the red line. Nearly 105% of the radiation dose can be applied at the ipsilateral thyroid gland, which is more irradiation than administered to the supraclavicular lymph node.

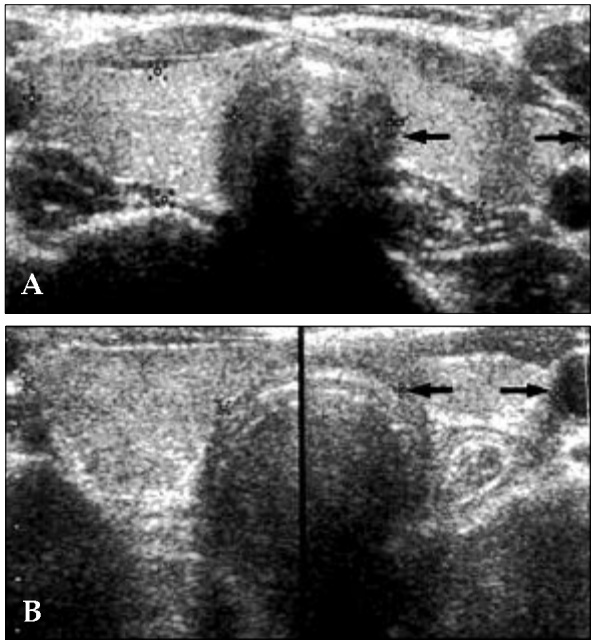


Fig. 4. (A) (pre-op) Initial measurement of thyroid gland before Hockey Stick irradiation of a left breast cancer patient. Transverse diameter was measured from the medial border of the common carotid artery to the lateral border of trachea (←~→: 2.3 cm). (B) A 47 year-old received left breast partial mastectomy 2 years previously and left Hockey Stick irradiation over 1.5 years. The size of the left thyroid gland of the same patient was considerably reduced after the radiation treatment (←~→: 1.6 cm).

The purpose of this study was to identify the effects of supraclavicular lymph node irradiation, using the Hockey Stick method, upon the ipsilateral thyroid gland of post-operative breast carcinoma patients.

MATERIALS AND METHODS

Seventy-seven patients with breast carcinoma who received Hockey Stick irradiation after mastectomy were evaluated from 1999 to 2001. Thirty-nine patients underwent partial mastectomy, and 38 patients total mastectomy. Of these, 41 patients had primary breast carcinoma of the right breast, and 36 patients carcinoma of the left breast. All patients were treated with postoperative Hockey Stick irradiation, which was started at 2 to 6 weeks after mastectomy. The radiation fraction size was 2 Gy/day (Gray=Gy), and the weekly fraction size was 10 Gy, and total dose ranged from 44 Gy to 54 Gy (median 50 Gy).

We evaluated changes in the dimension of the ipsilateral thyroid gland size annually. The size of the thyroid was measured ultrasonography and the measurements were compared pre- and post-radiation therapy. Thyroid gland size was calculated from its greatest diameter in the axial plane from the lateral border of the trachea to the medial margin of the common carotid artery.

The echogenicity of the irradiated thyroid gland was also compared with the contra-lateral non-irradiated thyroid gland.

The patients irradiated by the Hockey Stick method were composed of; 77 patients at the one year follow-up, 37 patients at the two year follow-up and 21 at the three year follow-up (Table 1). As a control group, 31 breast carcinoma patients who did not receive postoperative radiation therapy were selected, and changes in their ipsilateral thyroid gland sizes were followed up annually for 3 years after mastectomy. Statistical analysis was performed using the Wilcoxon signed rank test.

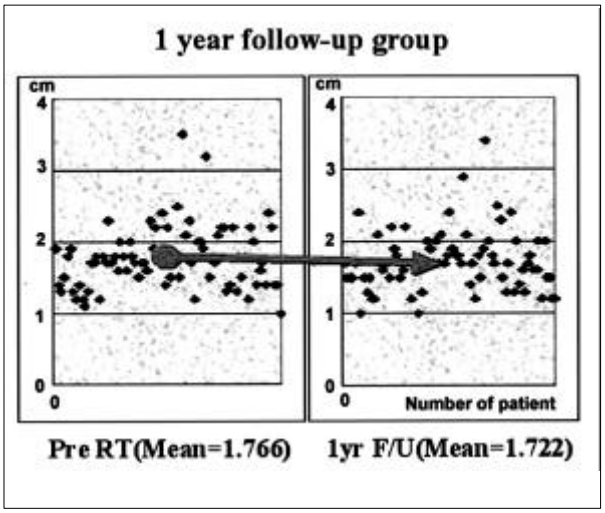
RESULTS

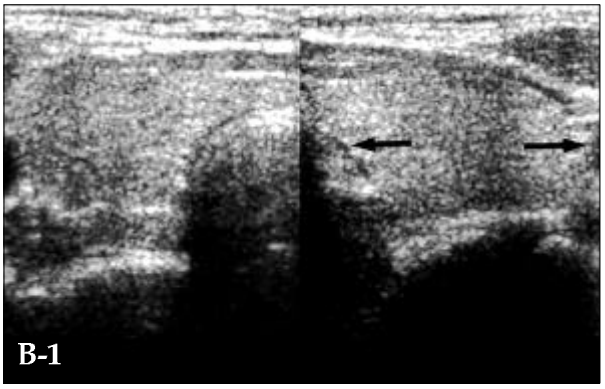
In the one-year follow-up group (n=77), the number of ipsilateral thyroid gland increases and reductions were almost equal. 41.5% of patients (n=32) showed an larger thyroid gland after Hockey Stick irradiation therapy, and 41.5% of patients (n=32) a smaller size. Only 16.9% of patients (n=13) showed no size change pre-versus post-irradiation. Fig. 5A, shows diagrammatically changes in the thyroid sizes of the first follow-up group (Fig. 5B-1 and 5B-2) patients (p=0.428). There show no definite changes of thyroid echogenecities in this group.

In the two-year follow-up group (n=37), 26 of the 37 patients (70.3%) showed a size reduction after Hockey Stick irradiation therapy (Wilcoxon signed rank test, p=0.001). Of these 18 patients showed a reduction of over 3 mm (a 3 - 4 mm decrease in 8 patients, and >5 mm decrease in 10 patients). Eight patients (21.6%) showed an increase in size and three patients (8.1%) showed no change after radiation therapy, which was very significant. Fig. 6a presents thyroid size changes determined at the two-year follow-up, and shows that even those patients who experienced size increases (Fig. 6B-1 and 6B-2) over the first year of thyroid irradiation, experienced a reduction at the 2 year follow-up (n=26)(Fig. 6B-3), and at the 3 year follow-up (n=15). In addition, 21 patients in the 2-year follow-up group (56.7%) showed increased echogenicity of the ipsilateral thyroid gland. This increased echogenicity was pathologically proven by US guided needle aspiration biopsy, the cell pattern of decreased cellularity with fibrotic fragement is consistent with post- irradiation fibrosis

Table 1. The Number of 1-Year, 2-Year and 3-Year Follow-up and Follow-up Loss Patients

	1 year follow-up group	2 year follow-up group	3 year follow-up group
Total number of follow-up patients	77	37	21
	after 1 year follow-up	after 2 year follow-up	after 3 year follow-up
The number of follow-up loss patients	40	16	0





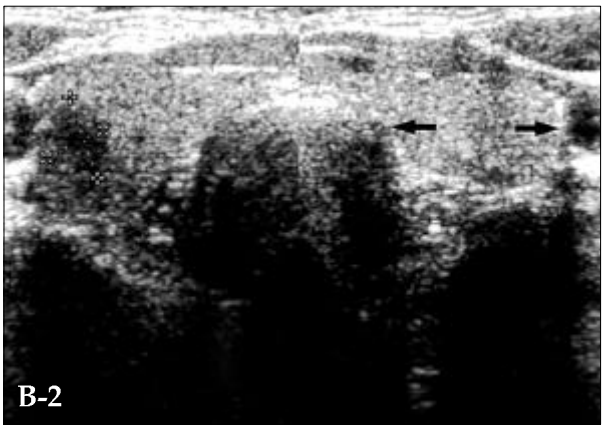


Fig. 5. (A) Graph illustrating the change of ipsilateral thyroid sizes of pre- and post-operatively irradiated one year follow-up group patients, showing increased (41.5%) and decreased thyroid size (41.5%). (B-1) (pre-radiotherapy) This 54 year-old woman had a partial mastectomy and received Hockey Stick irradiation to the left chest wall and neck. Preoperative measurements of the right and left thyroid gland were normal (←~→3.2 cm), and internal echogenecities were homogeneous and normal. (B-2) (1 year F/U) The same patient showing reduced left thyroid gland size after 1 year of Hockey Stick irradiation therapy of the left chest wall and neck (←~→: 1.8 cm).

comparing to non-irradiated normal thyroid gland (Fig. 6B-4).

In the three-year follow-up group (n=21, Fig. 7B-1), 15 patients (71.4%) showed a reduction in the ipsilateral thyroid gland size after irradiation therapy (Fig. 7B-2 and 7B-3). Eleven of the 15 patients experienced a reduction of over 3 mm (3-4 mm in 5 patients, >5 mm in 6 patients, p value= 0.005). Four patients (19%) experienced an increased in thyroid gland size and 2 patients showed no change (Fig. 7A). Increased echogenicity of ipsilateral thyroid gland was observed in 14 patients (66.6%).

In the non-irradiated control group of breast carcinoma patients (n=31), changes in the size of the ipsilateral thyroid gland were not statistically significant over 3 years of follow-up (the p value at one year=0.893, at two years=0.056, and at 3 years=0.121). Fig. 8A shows expected changes in thyroid sizes in the non-irradiated control group. It was found than changes of thyroid size in the control group were unremarkble (Fig. 8B-1). No changes in the internal echogenicities of the non-irradiated breast carcinoma patients were observed (Fig. 8B-2).

Therefore, the majority of breast carcinoma patients (32/77 at the one-year follow-up, 26/37 at the two-year follow-up, and 15/21 at the three-year follow-up) after post-operative Hockey Stick irradiation therapy showed a reduction in ipsilateral thyroid gland size.

DISCUSSION

Several reports upon thyroid function after the exposure of a large proportion of the thyroid gland during local irradiation of the ipsilateral chest wall and neck in partially mastectomized patients have been published. According to the dissertation of Turner,[1] histologic changes occur in the thyroid gland after 2.25 Gy of radiation therapy, such as follicle cell and vascular damage. These workers also reported hypothyroidism as a complication of irradiation in over 40% of patients after 4 - 5 years of follow-up. Glatstein, et al.[2] and McHardy-Young[3] found a slight reduction in the thyroid gland reserve without distinct hypothyroidism after radiotherapy of tumors of the head

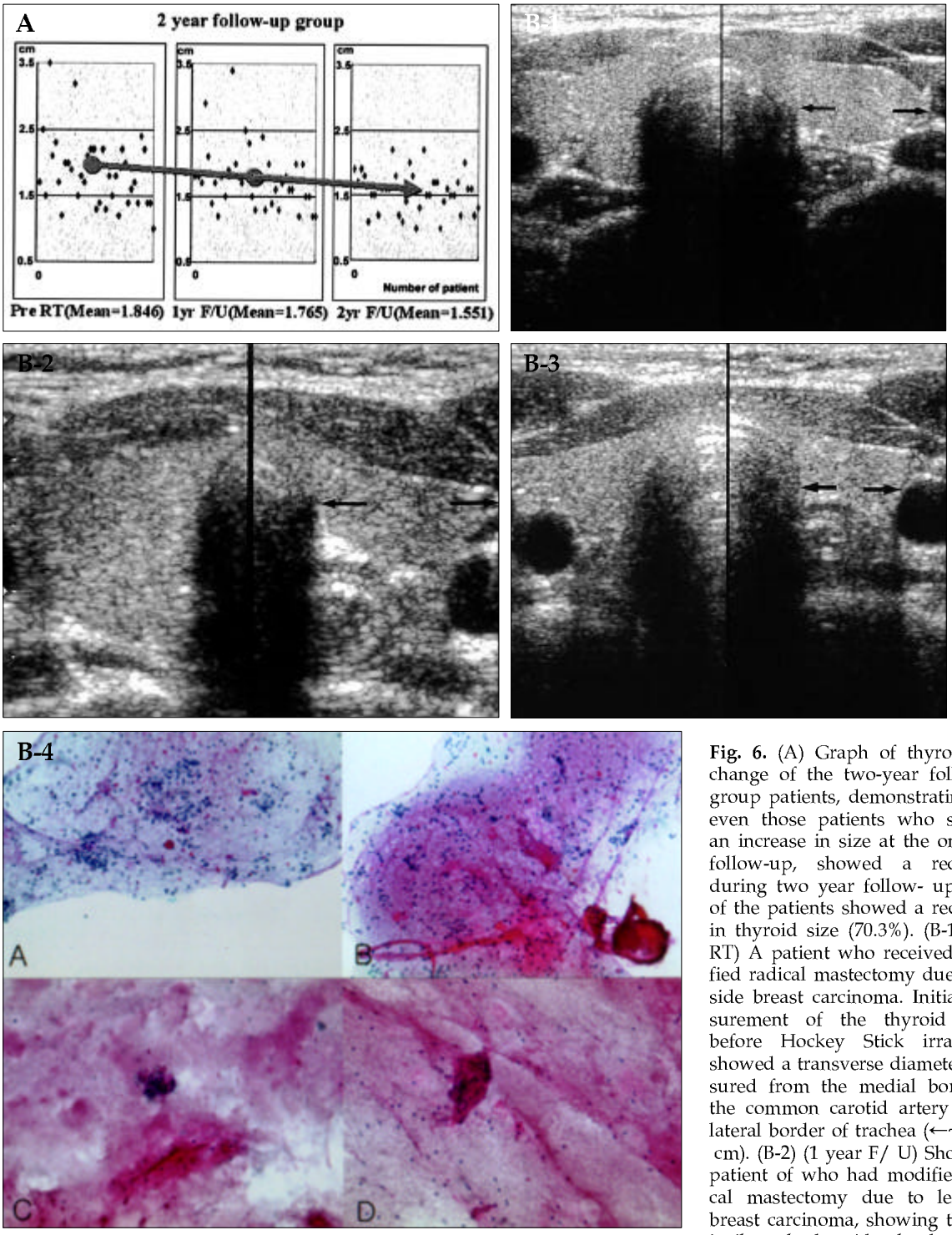


Fig. 6. (A) Graph of thyroid size change of the two-year follow-up group patients, demonstrating that even those patients who showed an increase in size at the one year follow-up, showed a reduction during two year follow- up. Most of the patients showed a reduction in thyroid size (70.3%). (B-1) (pre-RT) A patient who received modified radical mastectomy due to left side breast carcinoma. Initial measurement of the thyroid gland before Hockey Stick irradiation showed a transverse diameter measured from the medial border of the common carotid artery to the lateral border of trachea (←~~→: 1.9 cm). (B-2) (1 year F/ U) Shows the patient of who had modified radical mastectomy due to left side breast carcinoma, showing that the ipsilateral thyroid gland size is progressively reduced after Hockey Stick irradiation versus the pre-irradiated thyroid (←~~→: 1.67 cm). (B-3) (2year F/U) Again shows the patient of who received modified radical mastectomy due to left side breast carcinoma, showing that the ipsilateral thyroid gland was continuously reduced in size after Hockey Stick irradiation (←~~→: 1.43 cm). (B-4) (2 year F/U) The same patient as above. A fine needle aspiration biopsy of the right and left lobes of the thyroid gland was performed. A & B, Right thyroid gland reveals scattered clusters of normal inactive follicular cells (Papanicolaou × 200). C & D, Left thyroid gland demonstrates rarely found follicular cells with relatively frequent fibrotic tissue fragments (Papanicolaou × 200).

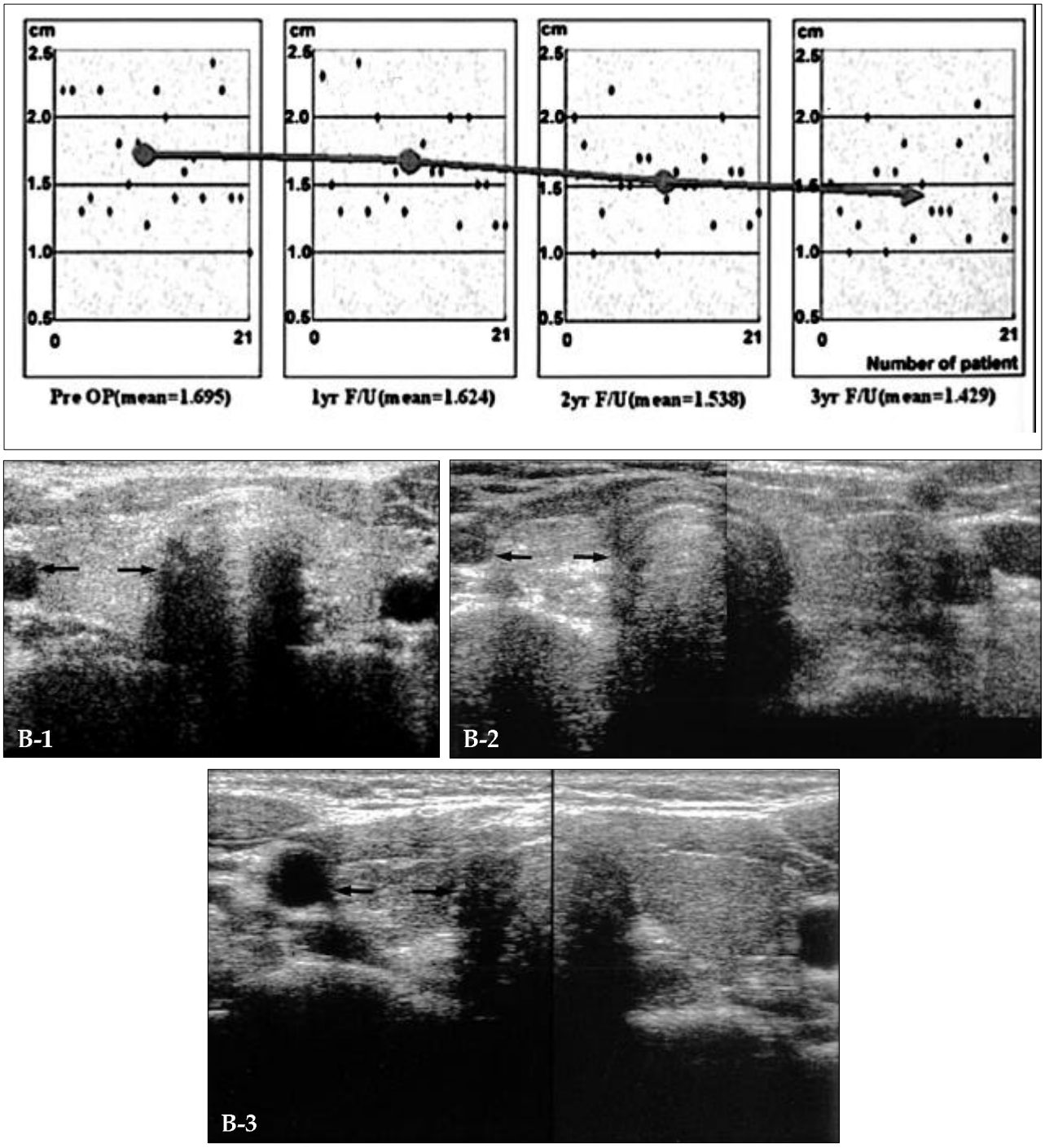


Fig. 7. (A) Graph showing thyroid size changes after two and three years of follow-up. In most of all patients, the ipsilateral thyroid gland sizes were reduced versus the pre-irradiated values. (B-1) (pre-RT) A 55 year-old woman with right side breast carcinoma who underwent post-operative radiation therapy. The initial measurement of thyroid gland size before Hockey Stick irradiation showed a transverse diameter (measured from the medial border of the common carotid artery to the lateral border of the trachea of 1.95 cm (←~→: 1.95 cm). (B-2) (1year F/U) The same patient as in Figure 7b-s above with right side breast carcinoma who underwent post-op irradiation. This case showed a right thyroid gland size reduction of ←~→: 1.52 cm, and demonstrates that the internal echo of the right thyroid gland increased, probably due to fibrotic change after radiation therapy. (B-3) (3 year F/U) The same patient as in the above, showing a reduced right thyroid gland, and an increased internal echogenecities of the right thyroid gland, probably due to fibrotic changes due to irradiation (←~→: 1.33 cm).

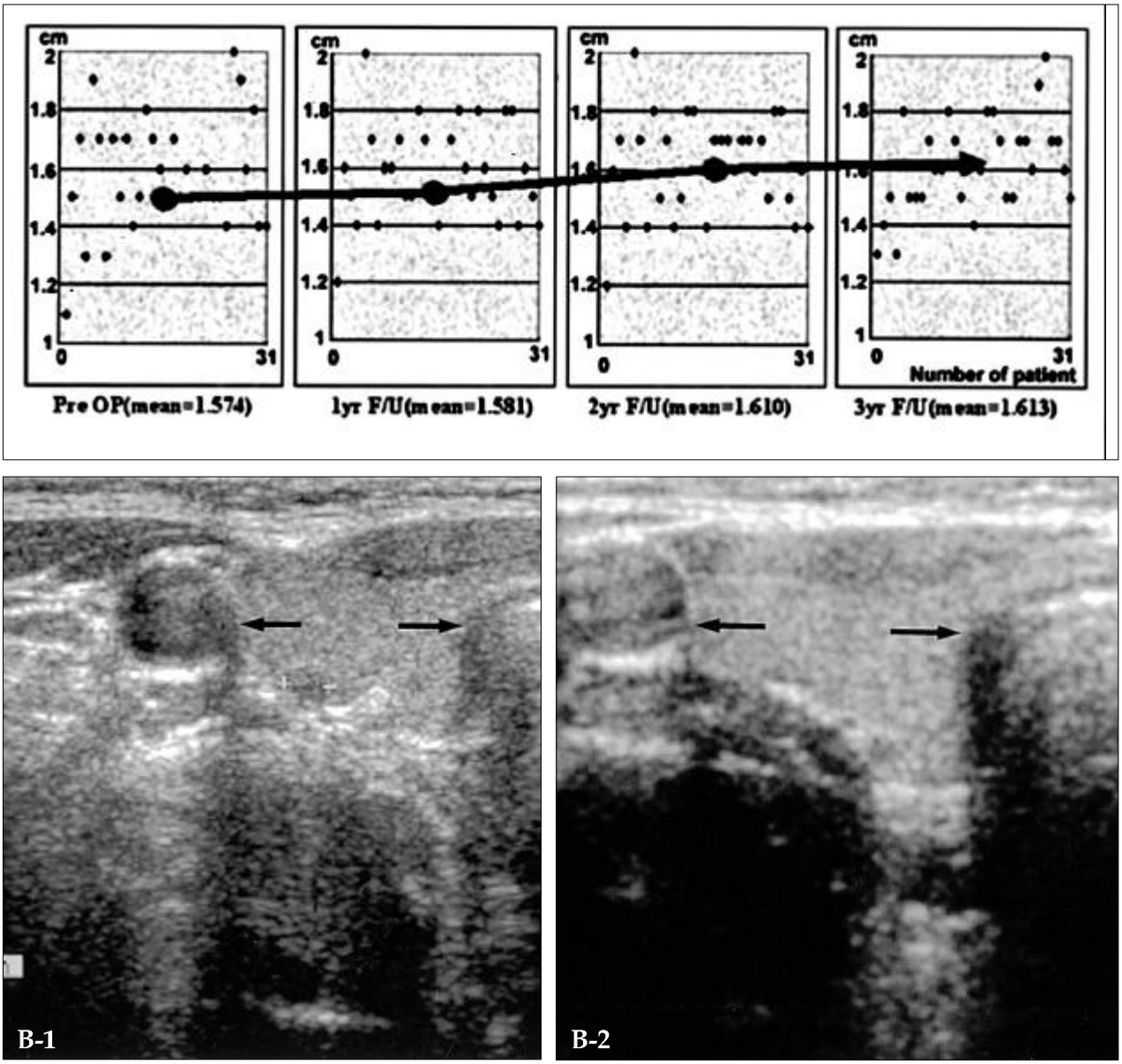


Fig. 8. (A) Changes in the ipsilateral thyroid gland size of the non-irradiated breast carcinoma patients, showing no significant changes in thyroid gland size over 3 years of follow-up. (B-1) (pre-RT) Showing no definite interval change in the right thyroid gland size in the non-irradiated left side mastectomized patient due to breast carcinoma (←~→: 2.21 cm). (B-2) (3 year F/U) Showing no definite interval change of the right thyroid gland size in non-irradiated left side mastectomized patient due to breast carcinoma (←~→: 2.22 cm).

and neck, our current results agree with these findings.

In our present study, the 2 and 3-year follow-up groups, of patients post-irradiated using the Hockey Stick method, showed that changes of the ipsilateral thyroid gland are closely related to irradiation therapy. Even though results after 1-year of follow-up were not statistically significant, the statistical results supported this relation at the 2-year follow-up (2 year follow-up group: p= 0.001, 3 year follow-up group: p=0005). We believe that post-irradiation reactions, such as edematous changes, over the first year of the radiation therapy explain this result. However, no thyroid biopsy was performed in the present study and therefore an exact diagnosis was not possible in

1 year follow-up group. But, in 2 year follow-up group, increased echogenicity was pathologically proven by US guided needle aspiration biopsy, the cell pattern of decreased cellularity with fibrotic fragement is consistent with post-irradiation fibrosis comparing to non-irradiated normal thyroid gland. As a control group, the non-irradiated breast carcinoma group revealed no significant thyroid gland size change during the 3-year follow-up (Fig. 8A). We did not evaluate the thyroid hormone level in our patients, though we suspect a relation between decreased thyroid gland size and thyroid hormone level changes. Other reports have revealed hypothyroidism after radiation therapy in postoperative breast cancer patients.[4-6] It has been said that hypothyroidism is to be expected, not only in cases of external irradiation involving the exposure of a small part of the normal thyroid gland, but also in cases involving the irradiation of a large proportion of the thyroid gland. Therefore, we would expect functional thyroid changes in irradiated breast carcinoma patients after ipsilateral thyroid irradiation in addition to hypothyroidism after neck irradiation, as has been reported in the literature. Samaan,[7] et al. evaluated thyroid dysfunction after radiation treatment and noted a 43.6% incidence of primary hypothyroidism after a period of one to 26 years in irradiated breast cancer patients. Although most of these patients were not clinically symptomatic, the authors advocated longitudinal follow-up to determine if the thyroid function continues to deteriorate.[8] A level of awareness of the frequency of abnormalities and their associated symptoms will aid appropriate patient management during follow-up. Many of the signs and symptoms of hypothyroidism are ill-defined and could easily be overlooked, particularly in postoperative patients, who show a high rate of comorbidity, and in whom the disease and its treatment may have nutritional, physical and psychological consequences that could easily mask the clinical features of hypothyroidism.[9,10] Close observation of irradiated postoperative patients would contribute to the detection of hypothyroidism, even though the condition may be asymptomatic. Further study to determine the relation between thyroid gland size and thyroid function would be helpful to devise a follow-up protocol for post-irradiated breast cancer patients.

Although routine supraclavicular lymph node irradiation using the Hockey Stick method improves the prognosis of breast carcinoma patients, the present study shows that the majority of these patients show a reduction in the size and increased echogenicity of the ipsilateral thyroid gland. The routine en face treatment of supraclavicular lymph nodes, using the Hockey Stick method, should therefore be reconsidered, and a close follow-up study of patients irradiated by the Hockey Stick method is warranted to prevent thyroid complications.

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