

## Planning of the Internal Mammary Field Based on Lymphoscintigraphy Localization before Postoperative Radiotherapy of Breast Cancer

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### ABSTRACT

**Background:** Internal mammary irradiation is still an issue of great debate. Although treatment of internal mammary lymph nodes was routinely given in the majority of randomized trials, data in its value are still limited.

The aim of this study is to determine the variability of position of the internal mammary lymph nodes using lymphoscintigraphy and to compare the dose of radiation that reaches these lymph nodes, the heart and lungs if only tangential fields are used.

**Material and Methods:** This is a prospective study that included 30 breast cancer patients treated in the department of radiation oncology of the Egyptian National Cancer Institute, Cairo University, planned for postoperative radiotherapy. Lymphoscintigraphy was done for all patients for detection of the exact site of the internal mammary lymph nodes. Dose volume histogram (DVH) was done to measure the dose to the heart using CT planning. Two plans were done for each patient, the first with internal mammary field (plan I), and the second without but with contralateral crossing of the midline by 1cm (plan II).

**Results:** The mean percentage of the internal mammary lymph nodes included in the internal mammary field (plan I) was 70.03% while in plan II it was 3.05%.

The mean dose percentage reaching the heart in plan I was 54.5% of total dose, while in plan II it was 9.16% of total dose with significant  $p$  value  $<0.001$ . The mean dose to the heart decreased as the heart volume increased, this significant difference between the 2 plans was maintained for the different heart volumes.

Also, the radiation dose to the heart in plan I varied significantly ( $p: 0.001$ ) between the right side vs the left side with a mean dose of 48.02% and 63.5%, respectively.

The mean dose percentage reaching the lungs in plan I and plan II was 46.53% and 24.5% respectively, with significant  $p$  value  $<0.001$ .

**Conclusion:** If irradiation of internal mammary chain is intended, then a direct internal mammary field should be used. The planning of internal mammary field should be adjusted according to lymphoscintigraphy so as to include most of the draining internal mammary lymph nodes. The risk of late cardiac and pulmonary complications will increase when using direct internal mammary field, but the risk of cardiac complications will be less in irradiation of right side internal mammary lymph nodes compared to that of irradiation of the left side.

**Key Words:** Breast cancer - Internal mammary radiotherapy - Lymphoscintigraphy.

### INTRODUCTION

Radiation therapy plays an important role in the management of patients with breast cancer either post mastectomy or post conservative surgery.

The randomized trials clearly show that post mastectomy radiotherapy substantially reduces the risk of locoregional failure and improve survival in patients with involved axillary nodes undergoing modified radical mastectomy [1].

Internal mammary irradiation is still an issue of great debate. Although treatment of internal mammary nodal area was routinely given in the majority of randomized trials, data on its value are limited and contradictory [2].

The addition of internal mammary field to tangential chest wall field increased the volume of heart and lung irradiated, which is the most important treatment factor that may lead to late cardiac toxicity.

Our study aims at determination of the variability of position of internal mammary lymph nodes using lymphoscintigraphy and to determine the percentages of internal mammary lymph nodes irradiated, the heart and lungs, if a separate internal mammary field is not added.

### MATERIAL AND METHODS

This prospective study included 30 breast cancer patients who attended the department of radiation oncology, National Cancer Institute (NCI), Cairo university for postoperative radiotherapy during the period from December 2001 to June 2002.

The indication for postoperative radiotherapy after mastectomy in the NCI during this period was based on St. Gallen, [3] recommendations:

- 1- Mass  $\geq$ 4cm.
- 2- Positive axillary lymph nodes  $>$ 3.

Internal mammary lymphoscintigraphy was done for all patients following mastectomy and before starting radiotherapy to visualize the site of internal mammary nodes for evaluation of its position in the direct internal mammary (IM) field.

#### *Injection Technique:*

The technique described by Ege [4] that entails injecting 0.5-1.0mCi (18.5-37.0mBq) of  $^{99m}\text{Tc}$  nanocolloid with a particle size ranging from 10 to 50nm in a volume of approximately 0.2ml. The patient is injected in the supine position. The point of administration is situated approximately 3cm inferior to the xiphoid process and 1-2cm medial to the mid-clavicular line on the targeted internal mammary side. An insulin syringe (1.0ml volume) is used coupled to a 22-gauge, 1 1/2" needle. The syringe is held 45° from the horizontal plane with the needle directed towards the axilla on the ipsilateral side. The goal of injection is to deposit the radio-colloid just anterior to the posterior rectus sheath at a position approximately 2-3cm below the skin. The depth of injection is controlled by applying tension to the skin and underlying rectus muscle with the free hand. The needle, therefore, traverses the skin, subcutaneous tissue, and rectus muscle, stopping short of the peritoneal cavity. A tactile sensation is experienced at the correct depth; it is perceived as "springy" resistance of the needle tip as one encounters the posterior rectus sheath.

Progressing beyond this point results in an intra-peritoneal injection.

#### *Injection Assessment:*

Immediately following administration of the radio-colloid, the injection site is imaged to ensure that the tracer has been delivered to the correct location. On an anterior view of the injection site, dispersion of the radio-colloid in the posterior rectus sheath ideally appears elliptical in shape. A superficial subcutaneous injection tends to be more spherical, and frequently allows visualization of intra-dermal lymphatics, primarily those draining to the axilla.

To verify the depth of injection, the supine patient is imaged in a cross table lateral position with the skin surface defined by a radioactive marker ( $^{99m}\text{Tc}$  point source). In this view, the skin marker should show a noticeable separation from the injected tracer. Overlap of the skin marker and injectate suggests a superficial injection.

An intra-peritoneal injection will show rapid dispersion of radio-colloid throughout the peritoneal cavity. If either a superficial or an intra-peritoneal injection has been administered, the patient should receive a second injection.

#### *Imaging:*

A low-energy, all-purpose, parallel-hole collimator fixed to a large-field-of-view gamma camera is used. An image of the injection site is obtained to verify the adequacy of the initial injection when the patient returns after 2 hours for imaging. Additionally, visualizing the diaphragmatic lymph nodes provides further evidence that the radio-colloid was correctly administered. This is particularly relevant when the more cephalic lymph nodes cannot be seen in a particular patient, since this is frequently a sign of nodal tumor infiltration.

For views of the internal mammary nodes themselves, if the injection site remains within the field of view, images are generally collected for time (450 seconds per view). If the injection site is not in the field of view, images can be obtained for counts and, generally, 100,000 counts will suffice.

An anterior image is accumulated over the thorax, with the sternal notch delineated by a  $^{99m}\text{Tc}$  point source marker. This view best dem-

onstrates the extent and degree of relative radio-colloid uptake within the internal mammary lymph nodes. Additional anterior image is obtained while the corners of the routine internal mammary field are delineated by  $^{99m}\text{Tc}$  point source marker (Fig. 1).

For localization of the depth of the internal mammary nodes, cross-table lateral view is acquired with the patient lying supine and supra-sternal, mid sternum and xiphoid process are marked by a  $^{99m}\text{Tc}$  point source and the camera face positioned exactly perpendicular to the thorax on the side under investigation.

#### *The Target Volume of the Internal Mammary (IM) Field:*

- 1- Initially all patients are planned with the original size of the internal mammary field (5x12cm).
  - a- The lateral is 5cm lateral to the midline.
  - b- The superior border abuts the inferior border of the supraclavicular field.
  - c- The medial border is the midline.
  - d- The length of the field is 12cm.
- 2- Internal mammary field is then changed according to the lymphoscintigraphy. This change is either:
  - a- Increase the width of field.
  - b- Increase the length.
  - c- Or both.

#### *Estimation of the Dose-Volume Histogram (DVH) CT Planning:*

Dose-volume histogram summarizes the dose being received by each of the structures of interest, which is the heart in this study.

#### *Three-Dimensional Treatment Planning for Each Patient by Done by Two Techniques:*

- 1- With a direct anterior field to the internal mammary field (plan I).
- 2- No separate internal mammary field but included in the tangential field of the chest wall (plan II).

For each patient, the percentage of the radiation dose to the internal mammary lymph nodes, the heart and the lungs were calculated for comparison between the 2 plans.

#### *Dose:*

The prescribed dose for treatment was 4500cGy in 20 fractions, 225cGy per fraction. Over 4 weeks, the dose and isodose curves were calculated by 3D planning system. In plan I, the dose to the direct internal mammary field was given for the first 10 fractions by photons and thereafter by 9 MeV electrons.

#### *Statistical Methods:*

Analysis was done using the "Statistical Package of Social Science" (SPSS) version 9.

Quantitative variables were summarized using mean and standard deviation, median, minimum and maximum.

Data of the studied two plans and their effect on the heart and lung was compared using Wilcoxon Signed Ranks Test.

## **RESULTS**

The clinical and pathological profile of the 30 cases is shown in table (1). The mean age of the patients was 45 years (range, 23-65). Fourteen patients had mastectomy for right breast cancer, while 16 had mastectomy for left breast cancer. Most of the patients (77%) had a grade 2 tumors, while the rest had grade 3 tumors. The mean number of the axillary lymph nodes dissected was 14 (range, 3-24), while the mean number of positive axillary lymph node was 5.8 (range, 0-20).

#### *Distribution of Internal Mammary Lymph nodes:*

Internal Mammary Lymph Nodes were Detected by Lymphoscintigraphy and Distributed as Follows:

- 1- Within the planned internal mammary (IM) field 5x12cm (plan I), the mean percentage was 70.03%  $\pm$ 31.
- 2- Within the tangential and supraclavicular field (plan II), the mean percentage was 3.05%  $\pm$ 9.4.

The mean depth of lymph nodes that were detected by lymphoscintigraphy was 2.06 $\pm$ 0.3cm.

The lateral distance from the mid-sternum toward the same treatment side ranged from 0.5cm to 4cm with a median of 2.5cm, while the lateral distance from midline to the contralateral side ranged from 0.75 to 1.6cm with median of 1.5cm.

*Dose to the Lymph Nodes:*

The calculated dose to lymph nodes in internal mammary planning field (5x12cm) ranged from 3995 to 4702cGy with mean dose of  $4510 \pm 171$ cGy, while the dose to those lymph nodes using tangential fields only ranged from 3000 to 4500cGy with mean dose  $3989 \pm 715$ cGy.

The calculated dose to lymph nodes outside the original planning field ranged from 305 to 2789cGy with mean of 887cGy.

To cover the internal mammary lymph nodes, the planning field was changed in 14 cases (58.3%). This change was either by crossing midline in 4 cases, increasing length in 7 cases, or both in 3 cases.

The calculated dose to internal mammary lymph nodes after extension ranged from 3829 to 5406cGy with mean of 4497cGy.

The calculated dose to lymph nodes outside the extended field ranged from 427 to 4815cGy with the mean changing from 887cGy to 4014cGy.

*Dose to the Heart:*

The dose reaching the heart by direct internal mammary field (photon and electron) and tangential field, ranged from 36.9% to 79.4% with a mean percentage of  $54.5 \pm 12.57$  of total dose, while the dose reaching the heart by planning using tangential fields only ranged from 3% to 16% with a mean percentage  $9.16 \pm 4.66$  of total dose, with significant  $p$  value  $< 0.001$ .

The mean dose to the heart decreased by increasing the volume, and the relation between the 2 planning techniques was kept significant for the different heart volumes. When 20% volume was included, the mean dose was  $2459 \pm 353$ cGy by using tangential fields and separate internal mammary field (plan I), while by using tangential fields only (plan II) it was  $320 \pm 79$ cGy. To 50% volume it was  $1129 \pm 844$ cGy and  $210 \pm 57$ cGy respectively, while for 80% volume it was  $293 \pm 113$ cGy &  $110 \pm 23$ cGy respectively as shown in table (2) (Fig. 2).

*Dose to the Lungs:*

The dose reaching the lungs by direct internal mammary field (photon and electron) and tangential field ranged from 3% to 71.1% with a mean percentage of  $46.53 \pm 14.73$  of total dose.

On the other hand, the dose that reached to the lungs by planning using tangential fields only ranged from 18.2% to 33% with a mean percentage of  $24.5 \pm 4.2$  of total dose, with significant  $p$  value  $< 0.001$  (Fig. 2).

*Differences between Right and Left Breast Patients as Regards the dose Reaching the Heart and Lungs in Different Plans: (Fig. 3)*

The radiation dose to the heart in plan I and plan II varied significantly ( $p: 0.001$ ) in irradiation of the right side vs the left side with a mean dose of 48.02% and 63.5%, respectively, in plan I, and 4.54% and 11.9% in plan II.

But there was no significant difference in the dose reaching the lungs between both sides in different plans.

Table (1): Clinical and pathological profile of the 30 cases.

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Age	Mean	45±8.9
	Range	23-65
Laterality	Right	14 (47%)
	Left	16 (53%)
Site in breast	Upper outer quadrant	10 (34%)
	Upper inner quadrant	4 (13%)
	Lower outer quadrant	7 (23%)
	Lower inner quadrant	3 (10%)
	Retroareolar	6 (20%)
Tumour size	T1	1 (3%)
	T2	10 (33%)
	T3	13 (44%)
	T4	2 (7%)
	Tx	4 (13%)
Grade	II	23 (77%)
	III	7 (23%)
The number of lymph nodes dissected	Mean	14.4±5.24
	Range	3-24
The number of positive lymph nodes	Mean	5.8±5.57
	Range	0-20

Table (2): Differences in doses to different volumes of the heart.

	Tangential fields + IM		Tangential fields only		$p$ value
	Mean	SD	Mean	SD	
20% heart volume	2459	353	320	79	$< 0.001^{**}$
50% heart volume	1129	844	210	57	$< 0.001^{**}$
80% heart volume	293	113	110	23	$< 0.001^{**}$

\*\* Highly significant.

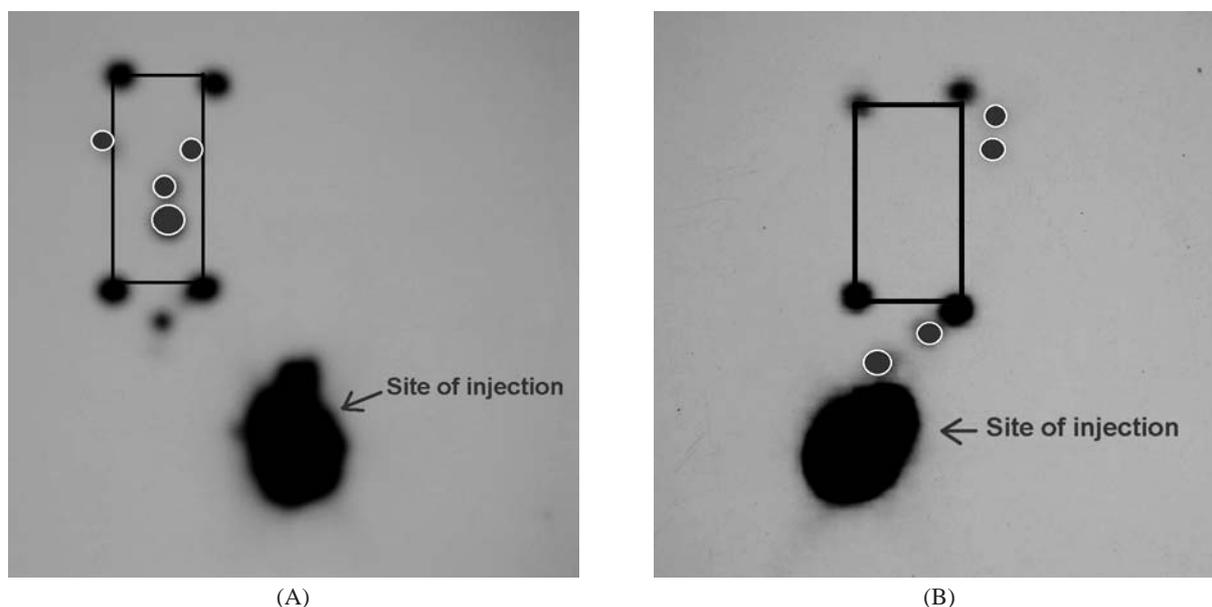


Fig. (1): Differences in the anatomical position of the internal mammary lymph nodes in 2 different patients, with most of the nodes included within the internal mammary field (IMF) in the first patient, contrary to the second patient with most of the nodes are outside the IMF.

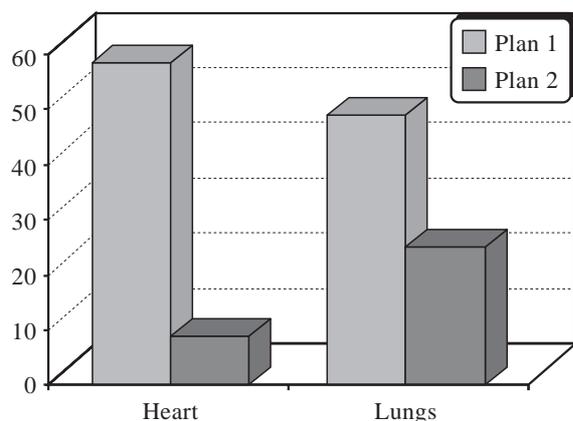


Fig. (2): Differences between the 2 plans as regards the dose reaching the heart and lungs.

P I : Internal mammary + tangential fields.  
 P II: Tangential fields only.

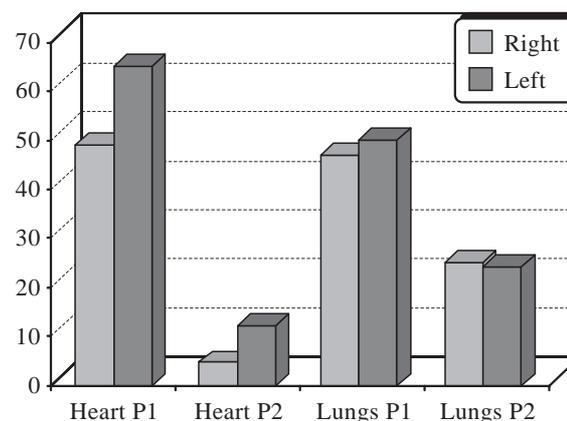


Fig. (3): Differences between right and left breast patients as regards the dose reaching the heart and lungs in different plans.

P I : Internal mammary + tangential fields.  
 P II: Tangential fields only.

### DISCUSSION

In the present study, the mean percentage of node distribution detected by lymphoscintigraphy within the planned internal mammary (IM) field, 5x12cm, was 70.03%, Struikmans and van Rijk [5] concluded that, by using lymphoscintigraphy, the internal mammary nodes included within the classical en-face limits of the so-called direct internal mammary irradiation field constituted only 47% of the retroclavicular nodes, which were usually outside the field in 34% and borderline in 19% of cases. According

to Bourgeois and Fruhling [6] only 78% came within the field, outside 15% usually related to the crossed drainage phenomena from one chain to the contralateral one, or to single contralateral IM chain and border line in 7% in the case of tangential fields.

Among 111 patients studied by Bentel et al. [7], the depth of internal mammary lymph nodes varied widely. It ranged from 0.8 to 6.2cm (median 2.4cm), the variation was found to be related to the patient's size represented by the anteroposterior diameter. Similarly, there was

great variability in the lateral distance of internal mammary nodes (range 1.7cm to 3.7cm, median 2.5cm). These findings match with our results as the mean depth of lymph nodes that were detected by lymphoscintigraphy was  $2.06 \pm 0.3$ cm, and the lateral distance from the mid-sternum towards the same treatment side ranged from 0.5cm to 4cm with a median of 2.5cm.

Danoff et al. [8], concluded that the average volume of the heart included in tangential field as determined by CT was 12% in left sided lesions and none in right sided ones. The addition of internal mammary field to the tangents increased the volume of the heart treated to 40%-60% in left sided and 17% to 24% in right sided lesions. This has been more confirmed in our study as the dose reaching the heart by direct internal mammary field (photon and electron) and tangential field, ranged from 36.9% to 79.4% with the mean percentage 54.5%, while the dose reaching the heart by planning using tangential fields only ranged from 3% to 16% with the mean percentage 9.16%. The radiation dose to the heart in plan I and plan II varied significantly ( $p: 0.001$ ) in irradiation of the right side vs the left side with a mean dose of 48.02% and 63.5%, respectively, in plan I, and 4.54% and 11.9% in plan II.

Gyenes et al. [9], reviewed the CT based planning of 100 consecutive left sided breast cancer patients. The prescribed dose to the tumor was 50Gy, the results showed that the mean irradiated heart volume that received at least 25Gy was 5.7% (SD=1.5%) for the whole group and 11.9% in those with highest volumes. They calculated that the volume of heart receiving a dose of 50% or more of the prescribed dose was, on average, only 5.7%, in contrast to our study, which showed that 20% of the heart volume received more than 50% of the prescribed dose when adding the internal mammary field. This is probably caused by different target definitions, leading to the more medially located medial border of the tangential fields used in their study.

Hurkmans et al. [10], performed three-dimensional treatment planning for 30 patients with left-sided breast cancer and various breast sizes. Two locoregional techniques (Techniques A and B) and a tangential field technique, including only the breast in the target volume,

were planned and evaluated for each patient. In both locoregional techniques, tangential photon fields were used to irradiate the breast. The internal mammary lymph nodes were treated with an anterior mixed electron/photon field (Technique A) or with an obliquely incident mixed electron/photon internal mammary field (Technique B). Both techniques resulted in a higher probability of heart complications compared with tangential irradiation of the breast only. They calculated the heart volume receiving a dose of 74% of the prescription dose and found that this volume was similar (average 7%, range 0-20% in technique A; average 5%, range 0-17% in technique B) compared with the data for their technique (average 5%, range 2-12%).

Irradiation toxicity of the lung was low in all techniques; the mean lung dose was an average 3.7Gy (range 1.7 to 6.1), 5.8Gy (range 3.3 to 9.9) and 3.8Gy (range 0.8 to 8.9Gy) for techniques A, B and the tangential field technique respectively. The dose reaching the lungs in our study was much higher either by direct internal mammary field (photon and electron) and tangential field (ranged from 3% to 71.1%) or by planning using tangential fields (ranged from 18.2% to 33%). This higher doses may be attributed to the increasing of the width and length of the internal mammary field to include most of the internal mammary lymph nodes seen outside the usual 12 x 5cm field after its detection by lymphoscintigraphy.

Pakisich et al. [11], reported average lung doses of 10.6, 15.2 and 16.1Gy (scaled to a total dose of 50Gy at the 100% isodose) for a tangential field technique adjacent to an anterior field covering the lymph node, a tangential field technique adjacent to an oblique field covering the lymph nodes and a technique using deep tangential fields, respectively.

Accordingly the internal mammary field cannot be treated properly except by using a separate internal mammary field adjusted by lymphoscintigraphy and using mixed beam. This is on the expense of high dose to the heart, the mean dose to 80% heart volume was 293cGy using tangential fields and internal mammary field while it was 110cGy using tangential fields only with highly significant  $p$ -value ( $<0.001$ ). Thus, it was quite evident that we should limit

internal mammary radiation field in only highly indicated patients as in central or inner quadrant tumors and highly positive axillary nodes.

It has been confirmed that adjuvant radiotherapy following mastectomy in some patients affects survival. In a Danish study [12], the high risk patients who were all receiving chemotherapy were randomized to radiotherapy or not. The irradiated volume included the internal mammary nodes. An overall survival benefit of statistical significance was found for the irradiated pre menopausal patients.

Roseman and James [13], studied the efficiency of adjuvant radiotherapy in medial breast cancers with negative axillary nodes in a retrospective study comparing a recurrence rate at 5 years of 42% after mastectomy alone compared with 18% after mastectomy and internal mammary node radiation.

In the previously mentioned 2 trials, internal mammary irradiation was given. Whether this could have an impact on survival or not is debatable, as Noguchi et al. [14], reported results in 25 internal mammary node-positive patients (after internal mammary nodes dissection on biopsy) treated by mastectomy and adjuvant chemo-endocrine therapy. The 10-year overall survival in internal mammary node-positive patients was 100% in the 4 patient with negative axillary nodes and 28% in the 15 patients with >3 positive axillary nodes. Thus it seems that the impact of axillary lymph nodes on survival is more than the internal mammary nodes.

Although there is some interest among radiation oncologists for the prophylactic treatment of the internal mammary lymph node chain due to the success of comprehensive post mastectomy radiation in recently reported large prospective randomized trials, yet there have been many other post mastectomy trials that have failed to show overall survival benefit or one that was statistically significant to radiation that included the IMN chain [15].

Data from two additional trials involving IMN irradiation is pending. The EORTC is conducting a trial in stage I-III patients with positive nodes, or medial/central quadrant tumors with positive or negative nodes. Patients are randomized to treatment of the breast (following conservative surgery) or chest wall

(following mastectomy) with or without radiation of the internal mammary and supraclavicular nodes. The National Cancer Institute of Canada (NCIC) conducted a similar trial in stage I-III patients consisting of conservative surgery and radiation to the breast with or without the regional nodes including the IMNS. Eligibility for this trial includes node positive patients, tumors over 5cm or tumors over 2cm. These randomized trials were designed to detect 5% improvement in overall survival for patients treated with regional nodal irradiation at 5 years in the NCIC trial and at 10 years in the EORTC trial [16].

It must be apparent that internal mammary nodal treatment is not of great value or that the subsets that benefit are quite small and thus far unidentified. A review of outcome in treated patients indicates that the major site of failure after local-regional treatment is distant metastases, and that there is a high correlation between nodal involvement and the presence of distant metastases. These observations emphasize the limitations of nodal treatment and the need to re-evaluate its use in the light of its efficacy and toxicity. We would like to stress that the importance of lymph node treatment should not be confused with the importance of treatment of the primary tumor, since there are data which indicate that the likelihood of distant metastases increase when the local breast tumor is treated inadequately [17].

#### *Conclusion:*

There is no evidence until now on who might benefit from internal mammary radiation in the adjuvant radiotherapy following mastectomy, and whether avoiding its use will affect survival or not.

If irradiation of the internal mammary chain is intended, then a direct internal mammary field should be used. The planning of internal mammary field should be adjusted according to lymphoscintigraphy so as to include all draining internal mammary lymph nodes. The risk of late cardiac and pulmonary complications will increase when using direct internal mammary field, but cardiac complications risk will be less in irradiation of right side internal mammary lymph nodes compared to that of irradiation of the left side.

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