

# Internal mammary node management in breast cancer. A review

David Vrana<sup>a,c,d</sup>, Jiri Gatek<sup>b</sup>, Karel Cwiertka<sup>a</sup>, Lucie Lukesova<sup>a</sup>, Pavel Koranda<sup>e</sup>

**Background.** Internal mammary nodes visualized during sentinel node biopsy for breast cancer, remain an unresolved management issue. Further, both internal mammary node (IMN) radiotherapy and biopsy have attendant risks and hence should be used with caution. The purpose of this review is to highlight the available data and evidence.

**Methods and Results.** A PubMed database from 1960 to 2012 using key words: internal mammary nodes, breast cancer radiotherapy planning, adjuvant radiotherapy, sentinel node biopsy in breast cancer and selected publications on the significance of internal mammary nodes in breast cancer treatment, published data and approaches used.

We found 14513 relevant papers and we selected 30 that clearly investigated the management of internal mammary nodes during sentinel node search. We focused on the incidence of IMN metastasis (6 papers), risk factors associated with IMN drainage (9 reports), management of IMN and the impact on disease free and overall patient survival (15 papers).

**Conclusions.** The evidence for breast cancer axillary nodes management is good but the data for other draining nodes such as internal mammary nodes are far less conclusive and further research is needed.

**Key words:** internal mammary nodes, breast cancer, radiotherapy, sentinel node

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<sup>a</sup>Department of Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

<sup>b</sup>Department of Surgery, Atlas Hospital and Tomas Bata University in Zlín

<sup>c</sup>Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc

<sup>d</sup>Toxicogenomics Unit, National Institute of Public Health, Prague

<sup>e</sup>Department of Nuclear Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc

Corresponding author: David Vrana, e-mail: [davvrana@gmail.com](mailto:davvrana@gmail.com)

## INTRODUCTION

Breast cancer is the most common cancer in women worldwide. However, improved patient care is leading to better outcomes and unchanged or reduced mortality in many countries. The reason for this may be new treatment targeted therapy, improved surgical procedures (resection margin and sentinel node biopsy) and radiotherapy techniques that preserve at-risk organs (intensity modulating radiotherapy, active breathing control). However, there are still areas where current approaches are inadequate and clear recommendations are not available. One of these is sentinel node detection, more specifically the problem of internal mammary node (IMN) detection during axillary sentinel node biopsy. The sentinel node procedure is based on the assumption that the first node detected is at highest risk for metastasis and that pathologic examination of the node, in the case of negativity, can be omitted with all the consequences of avoiding the increased risks of arm edema after axillary node dissection<sup>1-4</sup>. There is some consensus regarding axillary node procedures during sentinel node detection and adjuvant radiotherapy. However, the situation is different in the case when the radiocolloid flow is directed to higher axillary node levels (level III or infraclavicular nodes, supraclavicular nodes) and in the case of internal mammary node detection<sup>5-11</sup>. Cox et al.<sup>12</sup> provided some recommendations for IMN

management in 1960. The situation now is very different; the surgical procedure for sampling internal mammary nodes carries the risk of bleeding, the procedure is longer and demands on surgical experience greater. Involvement of internal mammary lymph nodes is associated with poor prognosis<sup>13-16</sup>. However, there are a number of options for managing internal mammary nodes visualized during sentinel node sampling. The first is the IMN sampling mentioned above with all the potential consequences of the procedure, the second is to perform PET/CT or other imaging technique (ultrasound, MRI) to check for possible macroscopic disease. In this case, we have to take into account that any imaging technique will only detect tumors larger than 5 mm and in the case of internal mammary node sampling, it is clear that the majority of these node metastases are microscopic. Uninvolved IMN are usually around 4mm in diameter. In general, imaging techniques do not appear appropriate for resolving the issue. The last option is to irradiate all such patients and finally there is also the option to ignore the IMN. However, in this case, patients can be understaged and consequently undertreated. As IMN are detected in only about 20-25% of cases during sentinel node detection, is it acceptable to radiate the internal mammary chain in 25% of all breast cancer patients? The reason for our concerns about internal mammary node irradiation is the possible consequences of radiotherapy. Radiotherapy may

reduce the number of local recurrences but due to the unavoidable radiation of healthy tissues and organs, we can cause acute (within 90 days), late and very late effects on these organs. We are aware, from extensive experience, of the acute effects of radiotherapy, such as skin erythema, pericarditis and acute pneumonitis. While new treatment modalities such as intensity modulated radiotherapy and respiratory tracking, can significantly reduce the risk of acute effects, the situation is different in the case of late effects (occurring more than 90 days after radiotherapy completion). There are no clear recommendations about late effects or dose limits for external radiotherapy. In the case of adjuvant breast cancer radiotherapy, we are talking about heart<sup>17</sup>, lung and the contralateral breast as organs at risk in radiotherapy planning (other organs like brachial plexus, thyroid gland and skin have to be considered in certain situations as well). In the case of the heart, the recommended dose limit for acute pericarditis is V40 less than 40%. However, in cardiomyopathy and coronary artery disease, the dose limits are much less defined<sup>18-23</sup>. There are limited data on possible delayed effects and further research is needed to set the limits for radiotherapy treatment purposes. The foregoing makes it clear that IMN radiotherapy may significantly increase the risk of heart radiotherapy delayed effects and the indication should be carefully considered. The reader should understand that all our considerations are based on the situation when IMNs are not macroscopically positive (clinically, on PET or CT). In the latter case, radio and chemotherapy would be clearly indicated.

#### **Incidence of IMN drainage and IMN metastasis**

First, we focused on the prevalence of IMN metastasis and predictive factors for IMN involvement, aiming to select a subgroup of patients who could benefit from IMN radiotherapy or IMN biopsy. The incidence of IMN drainage is about 20% and of these in about 20%, metastasis are found during the biopsy. Hence, it follows that the incidence of IMN metastasis in breast cancer patients is around 4-6%. However, in some subgroups of patients it may be 28-52%. Heuts et al.<sup>24</sup> evaluated the probability of pathologic positivity of IMN in the case of lymphoscintigraphic drainage into these nodes. Internal mammary nodes were detected in 20% of cases (196/1008). IMN sampling was performed in 139 cases and metastasis were found in 31 (22%) cases (31/139) showing that patients with IMN drainage have a significant risk for metastasis. In contrast to this high positivity ratio, Veronesi et al.<sup>25</sup> evaluated 663 breast cancer patients of whom 68 had metastasis in IMN (10.3%). Farris et al.<sup>26</sup> reported 14% positivity rate of IMN in patients with early stage breast cancer. Considering these different frequencies of IMN involvement there is a clear need to identify predictive factors which could select a subgroup of patients who could benefit from more extensive staging or adjuvant radiotherapy and chemotherapy. IMN metastasis without ALN metastasis is rarely found in early stage breast cancer according to Ramsay et al.<sup>27</sup>. Using certain combinations of risk factors, the incidence of metastasis in IMN could be 44-65% (ref.<sup>28-29</sup>).

#### **Factors associated with IMN drainage and metastasis**

Coombs et al.<sup>30</sup> described possible risk factors for internal mammary chain involvement. Drainage into IMN was detected in 18.4% (90/490). Of the 18.4%, metastasis was confirmed in 22.2% or about 4%. The risk factors for IMN involvement were: age under 35 years, tumor grading and lymphovascular invasion. The same problem was investigated by Hyndí et al.<sup>31</sup> who evaluated studies including more than 300 breast cancer patients where in cases of IMN drainage, internal mammary nodes sampling was performed. After review of 6 studies altogether 3,876 patients, these authors found that IMN drainage was present in 792 patients (20.4%). IMN biopsy was completed in 644 patients and this revealed IMN metastasis in 111 cases (17.2%). After statistical review, the pathologic positivity was associated with lateral quadrants of the breast, contrasting with the generally accepted rule that IMN drainage is much more often in inner quadrants and hence may not be correct. The strongest predictive factor for IMN involvement was positivity of axillary nodes ( $P < 0.00001$ ). Zeng et al.<sup>32</sup> evaluated 88 breast cancer patients with internal mammary node sampling and concluded that histological grade and lymphovascular invasion status were associated with micrometastasis in the IMN ( $P = 0.018$  and  $0.001$ ). Postma et al.<sup>33</sup> sampled 107 IMN with lymphoscintigraphy drainage into these nodes. In 14 cases, the IMN were pathologically positive for metastasis (13%). Leidenius et al.<sup>34</sup> evaluated internal mammary nodes in 138 patients (out of 844, 14% cases). Drainage was more often found in patients with medio-central tumors (81 of 399; 20%), tumors in lateral quadrants (56 of 585; 10%;  $P < 0.0001$ ) and patients without axillary metastasis (17% compared with 10% with metastasis  $P = 0.0006$ ) (ref.<sup>34</sup>). Galimberti et al.<sup>35</sup> sampled internal mammary nodes in 160 patients. In 146 cases (94.4%) internal mammary nodes were negative and in 14 (8.8%) metastasis was found. Of these 14 cases, 10 had positive axillary nodes at the same time, confirming again that axillary node positivity in the case of drainage to IMN is a strong predictive factor for IMN metastasis. Van der Ent et al.<sup>36</sup> investigated internal mammary chain metastasis in 256 patients. This paper reported IMN metastasis in 26.8% (11/41). The metastases in IMN were associated with axillary node positivity. IMN metastasis without axillary metastases were detected in only 7.3% (3/41). Huang et al.<sup>37</sup> evaluated IMN in 1,679 Chinese patients. Their conclusion was that there are certain groups of patients defined by a risk factor combination with higher than 20% risk for internal mammary node involvement: patients with more than three positive axillary lymph nodes, location of the tumor in medial quadrants and positive axillary lymph nodes, patients with tumors larger than 5 cm and age under 35 years, patients with tumors larger than 2 cm and positive axillary lymph nodes at the same time, patients with tumors larger than 2 cm and located in medial quadrants. These findings point again to the conclusion that ALN involvement is an important predictive factor for IMN involvement<sup>38</sup>. IMN drainage and/or positivity data are summarized in Table 1.

**Table 1.** Risk factors associated with IMN drainage and/or pathologic positivity.

Author	Number of patients	Risk factors for IMN drainage and/or presence of metastasis
Coombs NJ et al. 2009	90	Age <35 years, tumor grade and lymphovascular invasion
Hyndie E et al. 2012	3,876	Axillary lymph node positivity
Zeng J et al. 2012	88	Lymphovascular invasion
Postma EL et al. 2012	486	Smaller tumor size, non-palpability and a medial localization of the tumor
Leidenus et al. 2006	138	Location of the tumor mediocentral and laterally, negative axillary nodes
van der Ent FW et al. 2001	256	Axillary lymph node positivity
Huang O et al. 2007	1,679	Four or more positive axillary lymph nodes, patients with medial tumor and positive axillary lymph nodes, patients with T3 tumor and age under 35 years, patients with T2 tumor and positive ALN, patients with T2 tumor and medial tumor
Paredes P et al. 2005	55	Location of the tumors in the inner quadrants

### Management of IMN and impact on disease-free and overall patient survival-the evidence

Zhang et al.<sup>39</sup> went a step further to determine if there were imaging techniques that could be used for detecting positive IMN in a high risk group of patients with clinical N2 and N3. These authors used ultrasound, computed tomography, positron emission tomography/CT, and/or magnetic resonance imaging to identify 112/809 patients who presented with clinically positive internal mammary node disease (13.8%). Using these imaging techniques, we could avoid the higher morbidity during IMN sampling. Some physicians also stress however that lymph drainage is highly dependent on IMN radiocolloid injection technique. Paredes et al.<sup>40</sup> investigated internal mammary chain involvement in 369 patients of whom IMN was detected in 55 cases. In the case of subdermal injection, there was no drainage into IMN found. However, in the case of peritumoral injection, drainage was found in 15.9% and in 17.6% after intratumoral injection. The predictive factor for internal mammary chain drainage was location of the tumors in the inner quadrants ( $P < 0.001$ ). There are also data supporting the negative prognostic value of location of tumor in the inner quadrant<sup>41-42</sup>. This difference may be explained by lymph drainage to internal mammary nodes which are usually omitted during breast cancer patient staging and treatment. Several trials have failed to prove the advantage of surgical dissection of IMN for disease-free and overall survival<sup>43-44</sup>. As mentioned, the survival benefit is often not clear and patients may be exposed to unnecessary treatment and side-effects. There are few studies that have evaluated the benefit of IMN radiotherapy in the case of the absence of macroscopic disease in IMN as disease-free and overall patient survival. The data presented by Veronesi et al. have already been mentioned. Olson et al.<sup>45</sup> recently focused on this problem to determine the significance of radiating internal mammary nodes during adjuvant therapy. Node-positive for metastasis or T3/4 invasive breast cancer patients were included in the study. Altogether there were

2413 breast cancer patients. 41% had IMN included in the radiation field. After a median follow up of 6.2 years, the 5-year disease-free survival for patients with IMN radiotherapy and without the radiotherapy was 82% vs. 82% ( $P=0.82$ ), overall survival 85% vs. 83% ( $P=0.06$ ) allowing us to conclude that no statistically significant difference in survival was achieved by radiating IMN. Fowble et al.<sup>46</sup> irradiated internal mammary nodes in 114 stage I and II breast cancer patients and compared them to 1269 who did not. After 5 and 10 years follow-up there was no significant difference found in locoregional recurrence or metastasis. No difference was found for overall survival either. Kong et al.<sup>47</sup> found 334 patients with IMN drainage after a database research at the University of Texas MD Anderson Cancer Center between 1996 to 2005. On statistical analysis, no difference in overall survival was found. Stemmer et al.<sup>48</sup> investigated the outcome of high risk stage II and III breast cancer patients with or without IMN treatment. After 77 months of follow-up, the disease-free survival of the patients with IMN irradiation was increased (73% versus 52%;  $P=0.02$ ). However, no statistically significant difference was found for overall survival (OS; 78% versus 64%;  $P=0.08$ ). No overall survival differences were reported either by Koo et al.<sup>49</sup>, Fisher et al.<sup>50</sup>, and Arriagada et al.<sup>51</sup>. Overall survival and disease free survival are summarized in Tables 2 and 3.

### CONCLUSION

There are no recommendations available on managing internal mammary nodes during sentinel nodes detection even if metastases to IMN are associated with poor prognosis. We always have to weigh the benefits of radiotherapy against local and distant recurrence and balance this against possible late effects caused by adjuvant treatment, especially considering the longer over-all survival of the breast cancer population, caused not only by better treatment but also due to improving prevention and treatment

**Table 2.** Impact of IMN radiotherapy on DFS and OS.

Author	Number of patients (IMN radiotherapy/ total number)	Stage of the disease	Follow up	DFS impact	Survival impact
Olson RA et al. 2012	981/2413	Node-positive or T3/4N0	Median 74.4 months	82% vs. 82% ( $P = 0.82$ )	85% vs. 83% ( $P = 0.06$ )
Fowble B et al. 2000	114/1383	Stage I and II	60 and 120 months	No difference	No difference
Stemmer SM et al. 2003	100	Stage II-III	Median 77 months	73% v 52% ( $P=0.02$ )	78% v 64% ( $P=0.08$ )

**Table 3.** Impact of IMN drainage on OS.

Author	Number of patients (IMN drainage/total number)	Follow up	Survival impact
Kong AL et al. 2012	334/1772	Median 88.8 months	No difference
Koo MY et al. 2012	88/525	Median 107-118 months	No difference

of other internal comorbidities. Currently, radiotherapy for IMN should be indicated in the case of clinically or pathologically proved involvement of IMN and considered in the case of the presence of combined risk factors such as axillary node involvement, tumors located in inner quadrants and IMN drainage during sentinel node biopsy procedure.

## CONFLICT OF INTEREST STATEMENT

**Author's conflict of interest disclosure:** *None declared.*

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