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SHORT REPORT

Are we wasting our time with the sentinel technique? Fifteen reasons to stop axilla dissection

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Summary Originally, surgery for breast cancer involved removing the pectoral muscles and the regional lymph nodes. This drastic technique was based on Halsted's paradigm of continuous tumour spread via the lymph nodes. In the last century, the amount of surgery has gradually decreased as breast cancer has been recognised as a primary systemic, or partially systemic, disease. Nowadays, breast-conserving therapy is widely used, but axillary lymph node dissection (ALND) and the sentinel technique are still common. Can the patient also be spared such axillary surgery? We have assembled convincing arguments against ALND (and therefore also against the sentinel technique) based on the probability that positive lymph nodes are unlikely to metastasise and that removing them is redundant. At least a discussion of this topic is more than overdue, even if it may be too early to change behaviour.

Arguments against axilla dissection

1. *Can lymph node metastases metastasise*? The process of metastasisation is highly complex involving over 250 genes and multiple mutations and cell evolutions. The chances of a cell developing the specific properties to survive the dissemination process and establish itself as a metastasis in a new environment are small. Having gone through this complicated transformation, what is the likelihood that this cell retains the capacity to evolve yet again to successfully spread to another organ? If metastases may not be able to metastasise then leaving positive lymph nodes in the axilla may not be harmful.[1–3]
2. *A poor prognosis may not be genetically dependent on lymph node status*: At the gene expression level, microarray analyses of the primary tumour indicate that 60% of lymph

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node-negative tumours have a poor and 40% of lymph node-positive tumours have a good prognostic signature. Although lymph node status is a good indicator of prognosis this correlation may be masking the true nature of the metastases process.[4]

3. *The number of positive lymph nodes reflects tumour growth time*: The larger the tumour, the longer it has grown, the more likely that tumour cells have disseminated. There is also a near linear correlation between the number of lymph nodes and the size of the tumour (between 2.5 and 50.0 mm). The number of positive lymph nodes may therefore simply be a sign of longer tumour growth and greater cell migration.[5,6]
4. *The apparently stepwise development of metastases in lymph nodes indicates a long tumour growth period*: The frequency of micrometastases and macrometastases in one or more lymph nodes correlates with tumour size as well as the frequency of distant metastases. These processes of tumour progression take years and are probably independent.[6,7]
5. *Changing lymph node status does not improve survival*: Studies of preoperative adjuvant therapy show similar survival for patients with negative lymph nodes that have been reversed by chemotherapy and those that remain positive. Lymph nodes are therefore unlikely to be a filter or temporary barrier to continuous tumour spread.[8]
6. *Removal of lymph nodes does not affect long-term survival*: Two randomised control trials with 25–30 years follow-up indicate that clearing the internal mammary or axillary lymph nodes have no impact on long-term survival. Despite the lack of evidence for the benefit of both procedures, only internal mammary lymph node dissection is not routinely performed today.[9,10]
7. *Internal mammary node irradiation does not improve survival*: Studies also show that irradiating the internal mammary nodes in addition to routine axilla dissection does not affect survival.[11]
8. *Lymph node irradiation is no more effective than removal*: If treating lymph nodes is effective, then presumably more would be better. Studies have shown, however, that irradiating lymph nodes in levels I–III results in similar survival times to lymph node dissection in levels I–II only.[12]
9. *Clearing more levels of lymph nodes does not affect survival*: Studies also indicate that there is no additional survival advantage to clearing level III of the axilla compared with clearing only levels I and II.[13]
10. *Tumour location affects the frequency of lymph node metastases but not survival*: The Munich Cancer Registry data show that 25.8% of patients with a tumour in the medial breast have axillary lymph node metastases compared with 35.5% of patients with a lateral breast tumour. Despite the 10% difference, survival time is similar for both tumour locations.[14]
11. *Not all positive lymph nodes are removed*: If lymph node removal were necessary, then partial clearance should be unacceptable, but studies have shown that up to 30% of positive lymph nodes remain in the axilla following a standard level I and II dissection.[15]
12. *Survival after the sentinel technique is not better than after conventional axilla dissection*: Positive lymph nodes outside levels I–II are now detected by the sentinel technique and removed.[16] Nevertheless, the survival seems to be equivalent and not better than survival after the axillary clearing of levels I–II.[17,18] This supports the hypothesis that only a small impact, if any, of the positive lymph nodes that have not been removed may exist.
13. *Tumour size may be a stronger determinant of survival than treatment procedure*: Population studies and data from different countries increasingly show the significance of tumour size. Adjusted analyses demonstrate that disease stage is a more important predictor of mortality than differences in treatments. This suggests that the disease course is principally determined by tumour growth time.[19,20]
14. *ALND severely affects patients' quality of life*: If axilla dissection brings no significant survival advantage, then patients are suffering debilitating arm problems unnecessarily.[21]
15. *In the case of solid tumours, there is no convincing evidence of a survival disadvantage if positive lymph nodes are not removed*: In breast cancer, a positive margin, multifocal primaries and ipsilateral de novo carcinomas are well known causes of metastases. They explain the long-term benefit of postoperative locoregional radiotherapy.[22,23] The equivalence of regional therapy without axilla dissection and the small number of regional recurrences[24] support the hypothesis of a negligible effect of regional radiotherapy on survival. Our hypothesis is that distant metastases develop over time from disseminated tumour cells that originate from the primary and not from the lymph nodes.

Conclusion

Local, regional and distant progressions are processes initiated by tumour cell migration from the primary lesion. After initiation they develop independently. The frequency of these processes and the percentage of a posteriori systemic diseases depend among other things on the size of the tumour at the time of removal. Up to now no data have been available that show that the three types of progression can initiate secondary metastases. Although some studies show the benefits of lymph node treatment,[25,26] the results do not disprove the multiple arguments presented here. Our hypothesis is based on evidence from clinical trials and observations from molecular biology. We hypothesise that ALND and sentinel lymph node biopsies are redundant and that lymph nodes should only be removed if they are locally disruptive. Such a paradigm shift may be too early to change behaviour. But the discussion should be focused on that topic. First, it can accelerate the introduction of the sentinel technique even if a further reduction in radicality is possible. Second, it should motivate systematic reviews of this hypothesis with the plentiful available knowledge about breast and other solid cancers. Third, it should encourage prospective studies with long-term follow-up to shorten the time of a further reduction of the Halstedian concept of radical surgery.[27,28]

References

1. Nestl A, Von Stein OD, Zatloukal K, et al. Gene expression patterns associated with the metastatic phenotype in rodent and human tumors. *Cancer Res* 2001;**61**(4):1569–77.
2. Bernards R, Weinberg RA. A progression puzzle. *Nature* 2002;**418**(6900):823.
3. Tait CR, Dodwell D, Horgan K. Do metastases metastasize? *J Pathol* 2004;**203**(1):515–8.
4. Van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002;**347**(25):1999–2009.
5. Michaelson JS, Silverstein M, Wyatt J, et al. Predicting the survival of patients with breast carcinoma using tumor size. *Cancer* 2002;**95**(4):713–23.
6. Engel J, Eckel R, Kerr J, Schmidt M, Fürstenberger G, Richter R, et al. The process of metastasisation for breast cancer. *Eur J Cancer* 2003;**39**(12):1794–806.
7. Chu KU, Turner RR, Hansen NM, Brennan MB, Bilchik A, Giuliano AE. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? *Ann Surg* 1999;**229**(4):536–41.
8. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997;**15**(7):2483–93.
9. Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. *Eur J Cancer* 1999;**35**(9):1320–5.
10. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002;**347**(8):567–75.
11. Fowble B, Hanlon A, Freedman G, et al. Internal mammary node irradiation neither decreases distant metastases nor improves survival in stage I and II breast cancer. *Int J Radiat Oncol Biol Phys* 2000;**47**(4):883–94.
12. Louis-Sylvestre C, Clough K, Asselain B, et al. Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. *J Clin Oncol* 2004;**22**(1):97–101.
13. Sinha PS, Thrush S, Bendall S, Bates T. Does radical surgery to the axilla give a survival advantage in more severe breast cancer? *Eur J Cancer* 2002;**38**(11):1474–7.
14. Janni W, Rack B, Sommer H, et al. Intra-mammary tumor location does not influence prognosis but influences the prevalence of axillary lymph-node metastases. *J Cancer Res Clin Oncol* 2003;**129**(9):503–10.
15. Canavese G, Catturich A, Vecchio C, et al. Prognostic role of lymph-node level involvement in patients undergoing axillary dissection for breast cancer. *Eur J Surg Oncol* 1998;**24**(2):104–9.
16. Tanis PJ, Nieweg OE, Valdes Olmos RA, et al. Impact of non-axillary sentinel node biopsy on staging and treatment of breast cancer patients. *Br J Cancer* 2002;**87**(7):705–10.
17. Chagpar A, Middleton LP, Sahin AA, et al. Clinical outcome of patients with lymph node-negative breast carcinoma who have sentinel lymph node micrometastases detected by immunohistochemistry. *Cancer* 2005.
18. Veronesi U, Galimberti V, Mariani L, et al. Sentinel node biopsy in breast cancer: early results in 953 patients with negative sentinel node biopsy and no axillary dissection. *Eur J Cancer* 2005;**41**(2):231–7.
19. Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer* 2003;**106**(3):416–22.
20. Maggard MA, Thompson JE, Ko CY. Why do breast cancer mortality rates vary across states? *Am Surg* 2003;**69**(1):59–62.
21. Engel J, Kerr J, Schlesinger-Raab A, Eckel R, Sauer H, Holzel D. Predictors of quality of life of breast cancer patients. *Acta Oncol* 2003;**42**(7):710–8.
22. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;**353**(9165):1641–8.
23. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;**97**(2):116–26.
24. Veronesi U, Orecchia R, Zurrida S, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. *Ann Oncol* 2005;**16**(3):383–8.
25. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival—a Bayesian meta-analysis. *Ann Surg Oncol* 1999;**6**(1):109–16.

26. Bland KI, Scott-Conner CE, Menck H, Winchester DP. Axillary dissection in breast-conserving surgery for stage I and II breast cancer: a National Cancer Data Base study of patterns of omission and implications for survival. *J Am Coll Surg* 1999;**188**(6):586–95 discussion 595–6.
27. Morrow M. A survival benefit from axillary dissection: was Halsted correct? *Ann Surg Oncol* 1999;**6**(1):17–8.
28. Morrow M. Is axillary dissection necessary after positive sentinel node biopsy? Yes!. *Ann Surg Oncol* 2001;**8**(9 Suppl): 74S–6S.