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Point of View

Routine or Delayed Axillary Dissection for Primary Breast Cancer?

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Prophylactic lymph node excision has long been recommended for preventing axillary recurrence of primary breast cancer, and has more recently gained support from the finding that adjuvant systemic therapy preferentially benefits patients with axillary node metastases. Despite these justifications, medical opinion in many communities has become deeply polarised over the merits of routine axillary dissection. A factor likely to be contributing to this split is the popularity of prescribing adjuvant systemic therapy (usually tamoxifen) on an expectant basis. Since there has been no controlled assessment of the net benefits of axillary dissection in patients receiving routine adjuvant systemic therapy—followed where necessary by delayed ("salvage") axillary treatment—objective data are urgently needed. If no substantial benefit is lost by replacing routine with delayed dissection, a small but significant improvement in quality of life could be expected for the majority of breast cancer patients.

Key words: breast neoplasms, axillary dissection
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INTRODUCTION

AXILLARY LYMPH node dissection does not significantly improve survival of breast cancer patients [1], and is thus most accurately regarded as a staging procedure. Nonetheless, since adjuvant treatments are of greatest potential value in high-risk disease [2], axillary staging may confer indirect antimetastatic benefits. For this reason alone, a level 2/3 axillary nodal dissection has now become routine in most academic breast oncology units [3].

With the popularisation of adjuvant tamoxifen therapy in recent years, however, many surgeons are questioning whether this policy of routine dissection—with its associated costs, morbidity and lack of survival benefit—remains justifiable on prognostic grounds alone. Moreover, few studies have assessed long-term local control following either adjuvant systemic therapy or delayed axillary treatment. Breast cancer clinicians are, therefore, increasingly faced with the question: should routine axillary dissection continue as an essential component of breast cancer management, doubly justified by considerations of local and distant relapse? Or has this brave new world of routine adjuvant drug therapy transformed node dissection into an unnecessary staging ritual?

AXILLARY DISSECTION AND LOCAL CONTROL

All asymptomatic axillae are asymptomatic in the same way, but each symptomatic axilla is symptomatic in its own unique way. The notion that all axillary recurrences present similarly dire management problems is a hangover from the Age of Mastectomy, during which most "local recurrences" involved chest wall infiltration. This phenotype portended a life expectancy comparable to that associated with distant relapse, while also raising the spectre of uncontrolled local failure [4]. Conversely, the sinister reputation of postmastectomy recurrence is a testament to the efficacy of radical surgery in preventing "good-prognosis" (salvageable) locoregional relapses. While intramammary disease is the most obvious example of the latter, isolated axillary recurrences also fall into this category [5]. Consistent with this, most isolated axillary nodal recurrences occurring after breast conservation are well controlled by surgery or radiation [6, 7], whereas refractory nodal relapses are typically complicated by co-existing distant disease [4].

The advent of breast conservation has thus brought with it a sea of change in the connotation of "local recurrence". Isolated axillary relapses are now regarded as relatively benign, with available data suggesting that the natural history approximates that of a second primary node-positive primary breast cancer [8]—an equation validated by superimposing the survival curves of axillary recurrence following late salvage [9] over those associated with primary node-positive disease [2]. Hence, the accepted efficacy of routine axillary dissection in preventing local nodal recurrence [3, 6] does not provide strong support for this policy.

SUBCLINICAL VERSUS CLINICAL NODE INVOLVEMENT

If there is one take-home message from the last century of breast cancer therapeutics, it is that local measures do not

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fundamentally transform the natural history of the disease. Improvements in disease control following radical surgery [5, 10] suggested that tumour burden correlates inversely with prognosis, but this correlation is surprisingly weak: for example, 5 year disease-free survivals associated with node-negative tumours ≤1 cm or 1–2 cm (which differ in tumour volume by an order of magnitude) are 89% and 85%, respectively [11]. In practical terms, this means that patients with small tumours cannot be confidently spared adjuvant therapies without further characterisation of risk factors—hence the theoretical appeal of supplementary investigations such as axillary node biopsy. Tumour size is thus a poor index of disease biology, partly because it is a continuous (quantitative) variable and partly because the decisive (qualitative) changes governing neoplastic progression exhibit no clear relationship to tumour growth [12].

A similar lack of correlation between node size and disease outcome is suggested by prognostic comparisons of clinical and pathological nodal status. Fisher and associates showed that "true-positive" palpable axillary adenopathy has a similar prognostic significance to clinically occult pathological stage II disease, and that failure to treat the axilla does not prejudice survival [13]. A second line of evidence relates to occult breast primaries presenting with clinically evident axillary nodal metastases—a presentation with a far more favourable prognosis than metastatic involvement of other sites, with survivals equalling [14] or even exceeding [15] those of clinically "occult" node-positive breast cancer. The biology of node-positive primaries and isolated axillary recurrences thus remains similar despite major differences in nodal size, supporting the plausibility of delayed (as opposed to routine) dissection as an approach to managing axillary recurrence.

SYSTEMIC TREATMENTS AND ISOLATED AXILLARY NODAL RELAPSE

Local relapse rates are reduced—albeit to an extent as yet not clearly defined—by adjuvant systemic therapies. Reports of radiotherapeutic synergism with either hormone [16] or cytotoxic therapy [17] are consistent with evidence that systemic adjuvant therapies mainly reduce local and soft-tissue relapses [18]. Since these data do not specifically address axillary recurrence, assessment of that problem must first consider the local efficacy of routine dissection. Impressively, axillary relapse following node dissection occurs in as few as 1–2% of cases [6]. Only 35–40% of patients prove to be node-positive following complete dissection, however, while only 10–20% of patients relapse in the axilla if undissected [19, 20]—making the failure rate of dissection in "at-risk" patients approximately 10%. As many as half of such "failures" may have co-existing distant disease [4], leaving a net 5–10% incidence of isolated axillary nodal relapse. Since 70–90% of such recurrences are satisfactorily managed with delayed axillary dissection and/or irradiation [6, 7], the absolute incidence of uncontrolled isolated axillary relapse in patients treated with delayed dissection plus adjuvant systemic therapy seems likely to be indistinguishable from that attributed to routine dissection.

The disappointing failure of aggressive local therapies to transform the natural history of breast cancer spawned the default hypothesis that breast cancer's natural history is overwhelmingly determined by biological rather than anatomical factors [1]. This paradigm in turn suggested that adjuvant drug therapies were the most promising strategy for progress—an insight which has since produced the first clear survival enhancement for patients with established disease [2]. Since routine adjuvant systemic therapy has now become standard, such therapy logically becomes the basis upon which other (local) therapies form adjuncts, rather than vice versa.

AXILLARY NODAL INVOLVEMENT AND DISEASE BIOLOGY

All breast cancers are likely to have (qualitative) metastatic potential, but some take (quantitatively) longer to express it than others [21]. Conversely, although breast tumours with axillary metastases are often complicated by distant relapse, up to 20% of node-positive patients enjoy long-term survival [2]. At first glance, this suggests a curative role for axillary dissection, consistent with a sequential model of metastatic spread. However, the latter interpretation fails to explain why only half of all undissected node-positive axillae relapse [19]. Premature death from distant metastases is implausible, since at least contemporaneous relapse at the site of "primary" axillary disease would be expected.

Is this behaviour of axillary nodal metastases informative or merely anomalous? In contrast to metastatic node size, the number of involved nodes correlates smoothly with mortality from distant disease [22], conspicuously lacking any prognostic discontinuity between node-negative and node-positive. This relationship implies a stochastic continuum, and indicates that axillary involvement is more accurately viewed as a quantitative (probabilistic) index of tumour metastatic propensity rather than as a qualitative marker of metastatic phenotype. Hence, the prognosis of patients with few (1–3) positive nodes differs only marginally from that of "node-negative" patients [22]—a central observation since the majority of "node-positive" patients have only 1–3 involved nodes [23]. This prognostic (and, by inference, biological) continuity of the node-positive/node-negative spectrum explains why detection of occult micrometastases in "negative" nodes has failed to become routinely useful. Indeed, the very term "axillary staging" is inappropriate, since "stage" is, by definition, a discontinuous concept. For clinicians to equate the finding of one or two positive nodes with high-risk disease (and negative nodes with low risk) is at best simplistic, and provides little rational basis for routine dissection.

AXILLARY DISSECTON AND PROGNOSTIC BENEFIT

The value of prognostic factors is proportional to the size of the therapeutic benefits so dictated—benefits habitually overestimated by oncologists [24]. Patients with poor outlooks have potentially more to gain from therapeutic intervention *a priori*, and may be psychologically more motivated to undergo toxic treatment; conversely, however, aggressive poor-prognosis disease may be the least amenable to therapy. Axillary nodal assessment is highly effective in identifying the latter, since patients with 10 or more positive nodes do not benefit significantly from any standard adjuvant interventions. Yet how many physicians routinely refuse to prescribe adjuvant treatment for such patients?

The practical value of nodal staging has been further weakened in recent years by the emergence of competing prognostic and therapeutic alternatives. In the most impressive example of benefit, an "average" node-positive premenopausal patient undergoing 6 months' adjuvant cytotoxic therapy survives 10 months longer than an untreated control. However, the differential benefit between two cohorts receiving effective adjuvant regimens (chemotherapy or tamoxifen) should be substantially less than the latter figure. To what extent does additional knowledge of nodal status amplify this gain? Relapse-free sur-

vival following ovarian ablation in node-negative and node-positive disease appears improved by 9.4% and 10.5%, respectively, after 15 years follow-up, while the corresponding benefits for chemotherapy-treated patients after 10 years are 7.1% and 8.7% [2]. Since tumour variables other than node status provide positive correlations upon which to base adjuvant decisions, any survival gains attributable to routine axillary dissection can be reasonably expected to be less than even these humble differences.

AXILLARY DISSECTION AND ADJUVANT DRUG DECISION-MAKING

Approximately 30% of "good-prognosis" node-negative patients are dead or dying within 10 years of axillary staging [2]. Procedures with similar false-negative rates (such as axillary nodal evaluation by palpation [13]) have rightly been condemned as useless, and supplementary markers such as peritumoral lymphatic or vascular invasion (LVI) are now regularly used to enhance the predictivity of nodal status. Since the efficacy of adjuvant tamoxifen is established for most postmenopausal breast cancer patients—including those with node-negative and/or ER (oestrogen receptor)-negative disease [2]—many surgeons now avoid routine node dissection in this setting. It is in premenopausal disease, however, that the decision-making value of nodal staging excites most controversy.

Two recent therapeutic advances are relevant. Firstly, tamoxifen is effective as adjuvant therapy for ER-positive premenopausal patients, including those who are node-negative [2]. Secondly, ovarian ablation (including LHRH (luteinising hormone releasing hormone) agonists) is as effective as cytotoxic therapy in unselected premenopausal patients [2] and perhaps significantly more so in ER-positive patients [25]. Hormonal manipulation has thus become a rational first-line adjuvant strategy in ER-positive disease. Negative ER predicts ineffectiveness of adjuvant tamoxifen [2] and less benefit from oophorectomy [25], while being a poor prognosticator in its own right [26]; for these reasons, ER-negativity alone now seems as reasonable a criterion as any for recommending adjuvant chemotherapy in premenopausal patients. Accordingly, the most critical factor in premenopausal breast cancer is no longer node status but ER status—not because it is more powerful as a prognostic marker, but because its contribution to adjuvant therapeutic decision-making is far less ambiguous.

REAL AND THEORETICAL DISADVANTAGES OF AXILLARY DISSECTION

Losing one's axillary nodes is not a trivial matter. Arm morbidity is common, with one study reporting numbness in 70%, pain in 33%, weakness in 25%, arm swelling in 10%, stiffness in 10% and reduced quality of life in 39% of patients [27]. This represents a significant cost to be balanced against any proven or putative benefit.

Yet there may be an altogether different cost to be paid for node dissection. Predictors of treatment efficacy may not be critical for patients with metastatic relapse, since response or resistance may be readily apparent on clinical grounds. However, adjuvant drug treatment lacks any such response marker, meaning that many postadjuvant patients who relapse will do so with incurable distant disease and without knowledge of whether earlier therapy was appropriate. Detection of isolated axillary progression might thus enable rescue of some first-line adjuvant failures by flagging the need for "second-line adjuvant" therapy. Such monitoring of axillary status could be undertaken either in clinical stage II disease, where unequivocal local progression would indicate adjuvant failure, or else in clinical stage I patients developing *de novo* axillary relapse during or after adjuvant intervention. Confirmatory dissection could be carried out at the time of axillary progression in such patients, thus protecting against further local failure. Alternatively, axillary response to second adjuvant treatment could be observed, reserving local therapies exclusively for resistant disease. Hence, consigning the axillary lymph nodes to a paraffinised grave may be tantamount to throwing away a uniquely useful indicator of response—thus depriving a sizeable cohort of a second bite at the adjuvant cherry.

AXILLARY DISSECTION: CLINICAL EFFICACY VERSUS PATIENT DESIRABILITY

Fashion has always been an important factor in breast cancer decision-making. Patients and doctors alike are subject to the changing influence of fashion, although not necessarily of the same type or at the same time. In this context, "fashion" includes considerations relating not only to efficacy—however that term happens to be defined at the time—but also to real-world variables such as cosmesis, convenience, credibility, functionality and finance. Indeed, therapeutic efficacy is a poor predictor of therapeutic fashion precisely because the former term is based on a narrow set of outcomes which exclude many of the equally important concerns denoted by the latter. Many effective treatments come to languish with the passage of time: highly selective vagotomy for peptic ulcer, for example, or fundoplication for reflux oesophagitis. Similarly, in breast cancer, neither the local control gains of radical mastectomy [28] (now obligatorily described as "mutilating") nor the potent antimetastatic effects of oophorectomy [29] (now popularly dismissed as "castration") have managed to withstand the changing priorities of patients and doctors.

Hence, the last century has been a tough and at times dispiriting one for the breast cancer field, hampered as it has been by over enthusiastic claims (efficacy) and unrealistic expectations (quality of life). If radical mastectomy was the *Tyrannosaurus rex* of 20th-century breast cancer therapeutics, routine axillary dissection is the Komodo dragon: a vestigial descendant surviving within the opportunistic niche temporarily created by the adjuvant therapy juggernaut. The question before us in 1995 is not whether prophylactic axillary clearance is effective—since effective in one sense it clearly is—but whether adequate primary breast cancer treatment is now possible without routine dissection.

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