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Point of View

Prebiopsy Neo-adjuvant Endocrine Therapy for Breast Cancer to Prevent Post-surgery Trauma-induced Growth Factor and Immune-suppression Mediated Tumour Progression

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WITH THE incidence of breast cancer escalating, in part due to screen detected latent cancer [1], and little evidence of reduction in overall mortality, there is a need for a new direction.

It is 81 years since Joynes and Rous observed that surgical injury induces accelerated tumour growth [2]. Alexander and colleagues [3] have confirmed these observations (Table 1) and demonstrated that trauma-induced tissue repair cytokines, such as epithelial growth factors, are involved. These cytokines, when combined with the time related immunosuppression produced by surgery [4], could explain why increasingly radical surgery has failed to improve survival in the past. The recognition [5, 6] that radiation is followed by durable T cell depletion for more than 6 years (Table 2) could explain why radiation, though significantly reducing local recurrence, has no effect on overall survival and may also be a factor in the late (after more than 15 years) second cancers reported from some studies [7, 8].

In prostate cancer, a recent study has demonstrated that use of neo-adjuvant total androgen blockade has substantially reduced blood born tumour cell dissemination at the time of prostatectomy [9]. Such an approach in breast cancer could offer a new direction to overcome the deleterious effect of surgery during the unopposed oestrogenic phase of the menstrual cycle [10, 11], the effect of which is magnified by the degree of surgical trauma applied (Table 3), though even such minor injuries as needle biopsy and mammography may have some effect [10, 12].

There is evidence from overview meta-analysis [13] and randomised trials [14] demonstrating that endocrine and cytotoxic chemotherapy may have additive benefit, possibly because they act on different cell populations in the cancer (Table 4). In addition, as both endocrine therapy [15] and chemotherapy [16] can downstage primary tumours, used together as neo-adjuvant therapy they could enable less radical surgery to be performed. With increasing acceptance that it is safe to use endocrine therapy to treat benign breast disease and use it in trials for chemoprevention, the use of short term neo-adjuvant total oestrogen blockade before any surgical interference with any breast mass whether clinically or mammographically detected could be justified. Patients achieving complete remission would proceed to excision biopsy of

Table 1. Circulating tumour cell implantation at sites of trauma [3]

	Incidence of metastases*	No. of nodules
Skeletal muscle	2/10	1
Laparotomy scar	10/10	4.5
Normal bowel	0/10	—
Bowel anastomosis	10/10	3

*After 10^5 sarcoma cells by intracardiac injection.

Table 2. Irradiation induced T cell lymphopenia after breast cancer radiation treatment

	Absolute lymphocyte count ($\times 10^9$/l)*	T cells	CD4/CD8 ratio†
Pretreatment ($n = 34$)	2	55%	1.95
Immediate post ($n = 34$)	0.8	50%	1.68
12 month post ($n = 34$)	1.1	46	NA
5–6 years ($n = 20$)	NA	NA	1.59

*Reference [5]. †Reference [6].

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Table 3. Influence of surgery and menstrual cycle status on breast cancer survival [10]

	Unopposed oestrogenic phase (day 3–12)		Rest of cycle	
	n	% 10 year	*n*	% 10 year
Breast conservation	15	70	39	84
Mastectomy	60	52	135	85
≤4 cm tumour	65	57	155	87
>4 cm tumour	10	44	19	63
ER+ve tumours	43	57	102	81
ER–ve tumours	19	42	46	83
Lymph node negative	33	82	91	89
Lymph node positive	42	36	83	78

ER, oestrogen receptors.

Table 4. Opposing actions of endocrine and chemotherapy on ER+ve versus ER–ve breast cancer [13]

5 year survival	Ovarian ablation ($n = 167$)	CMF ($n = 165$)
All cases ($n = 332$)	62%	63%
ER ≥20 ($n = 138$)	75%	61%
ER <20 ($n = 100$)	52%	68%

tumour site, while non-responders would, after needle biopsy proof of diagnosis, proceed to neo-adjuvant chemotherapy (± radiotherapy). This approach would demonstrate functional evidence for each tumour's degree of endocrine and/or chemo sensitivity before definitive surgery, thus enabling a more rational policy for postsurgical adjuvant treatment.

The discovery that sex hormone withdrawal is associated with regeneration of the thymus and lymphocytosis [17, 18] and evidence that response to endocrine therapy [19] identifies a subgroup of functionally well differentiated tumours which are more likely to respond to immunotherapy (Table 5) provides an additional parameter of therapy worth exploring in endocrine sensitive tumours. The recent reports that bropiramine, an oral interferon inducer, can produce durable complete remission in superficial bladder cancer that has failed BCG treatment [20] makes this an ideal agent for such studies.

Review of the possible deleterious effects of surgical and radiation induced immunosuppression and trauma induced cytokine release on breast cancer, particularly those in patients with elevated levels of oestrogen, has led to the proposal that the current order of multimodality therapy be reversed with endocrine and immunotherapy before histological verification, followed by chemotherapy (± radiotherapy) before definitive surgery in non-responders.

Table 5. Influence of immunotherapy (lentinan) on progression free survival of breast cancer responders to hormone therapy [19]

	No. of cases	Progression free in primary tumour
Controls	16	13%
Lentinan polysaccharide	15	47%

χ^2 4.2, $P < 0.05$.

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