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Current Perspective

TNM: Therapeutically Not Mandatory

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ABSTRACT

Cancer survival may be inversely related to the speed at which a primary tumour grows and disseminates. Assessment of prognosis using surgical and/or radiological definition of disease extent, i.e. staging, has thus become a standard intervention in newly diagnosed patients, with the most popular framework being the tumour-node-metastasis (TNM) system. However, increasing use of biomarkers – non-TNM factors that predict therapeutic benefit, rather than adverse disease outcome – has weakened the decision-making dominance of TNM. This shift from risk-led to benefit-led practice is now starting to blur the time-honoured qualitative distinction between curable (M_0, early stage, adjuvant) and incurable (M_1, early metastatic, palliative) disease treatment strategies; the same biologic drug strategy may improve average survival outcomes by similar increments for two patients, one of whom is 'adjuvant' and the other 'metastatic'. Plausibly, then, biomarker-positive patients presenting with high-TNM (M_1) disease may enjoy the same, if not more, disease-free and/or overall survival benefit as conventional low-TNM (M_0) patients when treated with standard adjuvant interventions. Conversely, M_0 patients concerned by quality-of-life issues such as alopecia may in future be able to choose better-tolerated personalised drug regimens similar to those now used with survival benefit in palliative settings, even if such adjuvant regimens have not yet been validated by level 1 data. To these ends, a modernised decision-oriented disease staging system called METS (molecular/extra-primary/tumour/symptoms) is presented here.

1. Introduction

Throughout human history most cancer treatment has been surgical in nature. Biopsy necessarily precedes morphologic diagnosis and molecular characterisation of a tumour, while cure for many cancers continues to require resectability as a *sine qua non*. Excision also provides unique information about tumour size, vessel invasion and engraftment within draining lymph nodes, thus 'staging' the disease. The latter process is completed by a panel of radiologic and serologic tests which help to quantify the probability and speed of relapse or cancer-specific death. For most tumours, such staging has been based on the tumour-node-metastasis (TNM) classification, but the limitations of this staging system have been scrutinised by many in recent years.[1–5]

The main driver of change has been the advent of molecular biomarkers which either predict the therapeutic benefit of target-specific drug treatment, or else improve the forecasting of disease natural history over that based on anatomic criteria alone.[6–10] This changing interface between the old

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and new may create tensions in multidisciplinary teamworking: for example, a surgical oncologist may feel that a patient merits a certain postoperative treatment approach based on well-established TNM risk factors, whereas a medical oncologist may choose to recommend a different therapeutic strategy based on new scientific predictors of drug efficacy or resistance.[11–16] A series of steps to resolve this conflict are explored here, and a solution – in the form of a more user-friendly disease-profiling system named METS – is proposed.

2

2.1. *Ditch the 'cure' concept*

Life is a terminal disease. By definition, one can only be 'cured' of a lethal condition X by dying of another condition Y before X is detected to have recurred; even if cured of X, the proverbial clock towards death is still ticking. Hence, 'cure' remains at best a relative concept, and at worst a marketing gimmick that may damage professional credibility. To avoid overstating therapeutic claims, oncologists might best describe their treatment intentions not as 'insurance against death' (a seductive, even coercive, concept) but as 'attempts to buy time' – time without symptoms or toxicity (TwiST)[17] or quality-adjusted life years (QALYs) that exceed the expected duration without treatment.

Algorithms such as Adjuvant Online (www.adjuvantonline.com) quantify benefit as a percentage risk reduction for recurrence or death ten years after adjuvant intervention. But this is not the most useful statistic for patients or doctors who are trying to weigh the pros and cons of a given treatment: for example, the absolute benefit of a drug that delivers the same ten-year recurrence-free survival increment in a forty-year-old and an eighty-year-old is greater in the former, if only because of fewer competing causes of death. From an actuarial viewpoint it is straightforward to estimate the mean number of QALYs that a given intervention – whether radiotherapeutic prevention of local recurrence, say, or chemotherapeutic hazard reduction for metastatic death – confers for a given case.

Why, then, is this not already done? In part, the answer may lie in the rather modest absolute benefits calculated as the average for most adjuvant treatments. What average QALY advantage would be calculated for a woman receiving post-lumpectomy radiation for ductal carcinoma in situ? How many elderly patients will purchase adjuvant drug therapies if informed of the average net survival benefit over that obtained by receiving exactly the same drugs later in the event of relapse?

2.2. *Take the subjective out of survival*

The key word in the foregoing discussion is 'average'. Most oncologists do not counsel adjuvant patients in terms of average survival time gained, but rather in terms of increasing the hope of 'cure', which is absolute. The subtext is that if you are cured of a disease you are cured forever (notwithstanding that you will perish of something else within a few years or decades). Fig. 1A shows the customary way that oncologists present treatment outcome data by reading the survival graph

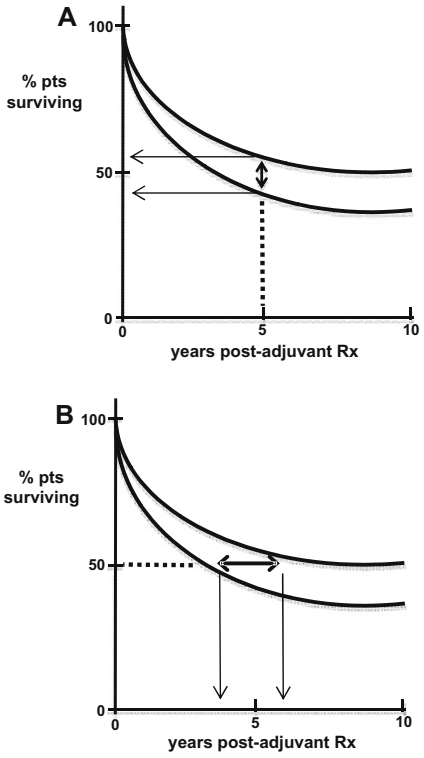

Fig. 1 – Different ways of presenting survival data. (A) Quantifying the size of the 'benefiting cohort'. The size of a putative 'treatment-cured cohort' can be measured by dropping a perpendicular from one curve to the next at maximum divergence. (B) Averaging the benefit across the total cohort. Using the same curves, the average benefit may be estimated by extending a horizontal line across at the 50% survival cut-off.

vertically. Irrespective of whether this distance represents 8% or 20% or 2% of the cohort, many patients will yearn to be included in this 'qualitatively distinct' cohort of drug-induced cures. Moreover, in those occasional cases where a patient may not be convinced by a low ten-year mortality benefit, the point may be won by showing a higher calculated risk and benefit for relapse.

In contrast, the 'quantitative average' benefit is shown in Fig. 1B by reading the graph horizontally. This shows that the average patient gains, say, ten months of survival (relapse-free or overall, depending on whether the ends of the two cancer-specific mortality curves eventually join up or not, respectively) in exchange for undergoing, say, five months adjuvant chemotherapy. This 'expected (average) gain' approach seems to be a more ethical way of presenting the treatment rationâle – and hence helping the patient to weigh up the desirability of purchasing and/or undergoing such treatment – than inviting the patient to gamble on perhaps becoming the lucky one of *n* treated to be cured.

Above all, since applicability of these 'horizontal' gains to overall and relapse-free survival alike implies relevance of these benefits to occult metastatic disease – curable and incurable, respectively – it is reasonable to expect that patients with early metastatic disease will enjoy similar benefits from 'adjuvant' treatments. It follows that if average benefits

can be quantified objectively, rather than being presented as 'the only possible way to increase your chances of being cured of cancer forever', conservative and/or cost-effective decision-making may become easier than it is in the present meliorist culture.

2.3. *Use PETs to upstage staging*

Most contemporary adjuvant outcome data accrue from the pre-PET era, implying that many of today's PET-defined M_1 patients would have been included in the previous M_0 cohorts. Although it seems desirable to have more sensitive delineation of disease extent, we should ask: how does this new generation of PET-positive patients – stigmatised as they are by the label of incurable disease – benefit from knowledge of what was hitherto occult disease? Is this new information cost-effective in terms of decision-making and survival/quality outcomes? And in such cases, should the oncologist abandon the adjuvant approach in favour of a purely palliative strategy; or should adjuvant-type treatment strategies continue to be considered, with or without modifications?

Most breast and bowel cancer patients treated in the past with adjuvant cytotoxic drugs have in fact had metastatic disease: surgically resected nodal metastases, admittedly, but metastases nonetheless. Is there any oncologist out there who confidently believes that a patient with 50 positive regional lymph nodes, even if PET-negative for distant disease, is 'non-metastatic' and hence readily curable? And does a node-negative patient with a single bone metastasis have a lower expectation of long-term survival, or of 'adjuvant' therapeutic benefit? Like the replacement of radical breast surgery by lumpectomy, the swift replacement of radical node dissection by sentinel node sampling[18] suggests that surgical ablation of low-volume metastatic disease makes less impact on survival than does optimal prescription of adjuvant treatment based on that information. The presence of early metastatic disease *per se* does not kill patients; rather, such disease highlights the risk that an unstable tumour genome may progress to a lethal phenotype months, years or even decades later. The widely accepted survival benefits of liver metastasectomy in colorectal cancer further emphasise that evidence of metastasis, even distant, should not trigger abandonment of efforts to improve the natural history of the disease.[19]

2.4. *Overcome the 'M_1' voodoo*

There are valid reasons for regarding the prognosis of M_1 carcinoma as hopeless, and hence subject to different (palliative) rules of intervention. For example, it has long been difficult to detect a survival advantage in diseases such as metastatic breast cancer treated with cytotoxic drugs alone[20] which, by default, leaves symptom relief as the only justification for active intervention. This negativity over the survival value of cytotoxics in advanced disease – a key factor underpinning the centrality of TNM in decision-making – contrasts with the oncology community's championing of survival benefits due to adjuvant cytotoxic therapy.[21] In theory, this discrepancy could be explained by the idea that cytotoxic drug therapy works more effectively on low-volume disease; indeed, there is dose-independent evidence that adjuvant chemotherapy confers more survival benefit in those patients who incur moderate normal cell toxicity.[22] The latter observation is consistent with the notion that cytotoxic disruption of fragile stromal-micrometastatic signalling, rather than direct killing of macrometastic cells sustained by stable autocrine networks, contributes to the survival benefits of adjuvant chemotherapy.[23] Consistent also with Smithers' view of cancer as a disease of normal cell interactions,[24] and with Fisher's model of cancer as a systemic disease,[25] this suggests that biologic manipulation is the most plausible strategy to improve survival in adjuvant and metastatic disease alike. Indeed, this has already been verified for hormonal manipulation[26] and trastuzumab-based treatments,[27] both of which – unlike cytotoxics alone – substantially improve survival in metastatic breast cancer.

Hence, in the new biological age, treatment benefit is likely to be determined less by TNM stage and more by biomarker profile. As such, medical treatment decisions can increasingly be made 'blind', i.e. without obsessing over previous black-and-white distinctions between M_0 and M_1 disease. Interestingly, biomarkers such as HER2 overexpression or E-cadherin (*CDH1*) gene deletion may also predict tumour metastasis patterns (to the brain and serosal surfaces, respectively), suggesting biomarker-led interventional strategies additional to those based solely on pharmacology.

2.5. *Put proportionality into perspective*

It is always easier to predict risk (of cancer recurrence or mortality) than benefit (of anticancer interventions), since quantifying benefit requires *a priori* estimate of risk but not vice versa. Partly for this reason, it has long been tempting for oncologists to assume that the benefit of an adjuvant intervention is a simple linear function of prognostic risk.[28] Biological factors modulate benefit independently of risk, however; this much is clear from the comparative hazard reductions and survival benefits achieved by chemotherapy in younger (7–11%; 10 months disease-free, 5 months overall) versus older (2–3%; 7 months disease-free, 3 months overall) breast cancer patients.[21] It is reasonable to hypothesise that there exist subsets of poor-prognosis (high-TNM) patients with drug-resistant disease in whom the benefit:risk ratio approaches zero, yet today's dogma of 'proportional benefit' insists that such patients gain the most from conventional treatment. Considered from first principles, the more likely reality is that absolute benefits from standard adjuvant chemotherapy are maximal in intermediate-prognosis cohorts in whom moderately aggressive disease remains moderately sensitive to drug treatments (Fig. 2).

Therapeutic decision-making is also limited by a paucity of therapeutic strategies. Until recently, the variety of combinatorial regimens that could be tailored for an individual's disease remained small, restricted to mixing DNA-damaging drugs in different schedules. With the arrival of biologically targeted drug therapies, however, the number of distinct treatment strategies is rising exponentially, including concurrent, sequential, maintenance and intermittent regimens. Furthermore, the dogma of 'proportional benefit' has all but evaporated with the advent of biomarker development: the

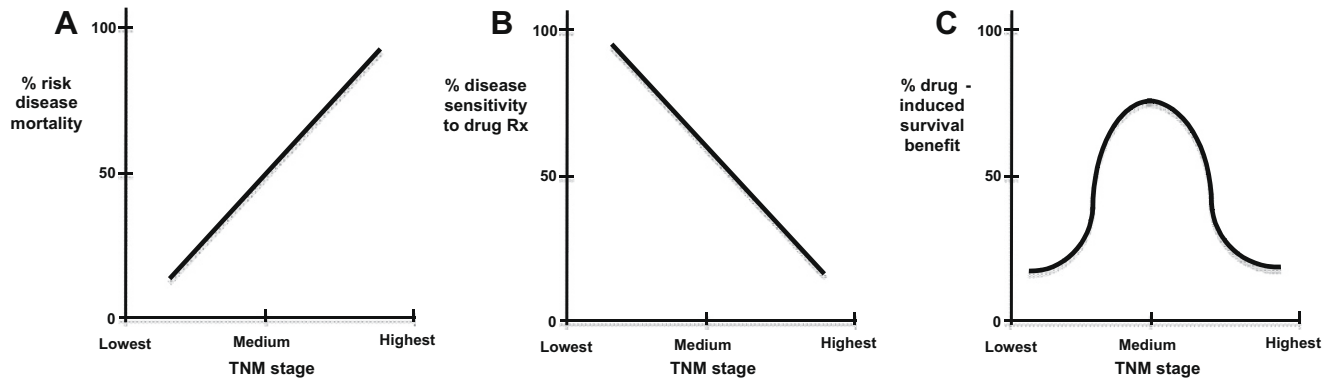

Fig. 2 – Model of benefit non-proportionality to TNM-stage risk in biomarker-positive patients. (A) Relationship of disease aggressiveness, based on TNM stage, to predicted disease-specific mortality risk. (B) Relationship of disease aggressiveness, based on TNM stage, to predicted disease responsiveness to drug therapies. (C) Relationship of disease aggressiveness, based on TNM stage, to predicted therapeutic survival benefit.

potential benefit of molecularly targeted drugs is primarily determined by biomarker profile, and only to a minor extent by TNM-based prediction of disease hazard. Indeed, the scientific credibility of biomarker-based treatment decisions (*vide* the accelerated FDA approval of imatinib for *Bcr-Abl*-expressing chronic myeloid leukaemia) may prove strong enough in future to make target-specific drug interventions acceptable even in the absence of high-powered randomized evidence for longterm survival benefit (Fig. 3). Since the therapeutic:toxic ratio of biologically targeted drugs tends to be higher for target-specific than for DNA-damaging drugs, the main factor limiting wider future use of such drugs in biomarker-positive disease will not be proof of benefit, but cost-efficacy. The historical dilemma of whether to use milder treatment regimens for low-TNM disease, reducing a modest benefit to minimal, will thus vanish in the biomarker-based treatment era, only to be replaced by more vexing cost-benefit issues.

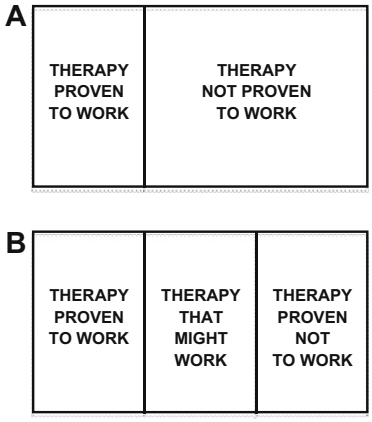

Fig. 3 – Changing paradigms of drug treatment. (A) Traditional western European model in which fiscal prudence within the welfare state dictates that a treatment of unproven efficacy is assumed to be ineffective until proven otherwise. (B) Evolving model in the era of biologically targeted new drugs in which only drugs proven to be ineffective are excluded from treatment algorithms. 'Drugs which might work' will include those targeted drugs for which a positive–predictive biomarker is expressed.

2.6. *Stage a comeback with METS*

For medical oncologists, the decision-making utility of traditional TNM staging will continue to decline with the rise of molecular profiling and target-specific drug therapies. A disease profiling system updated for the explicit purpose of drug decision-making algorithm could include the following components: (i) *m*olecular predictors of biologically targeted drug efficacy or resistance; (ii) *e*xtra-primary disease detection as an index of the need for drug (+/– local) therapies; (iii) *t*umour morphology as a predictor of the need for local (+/– drug) therapies and (iv) *s*ymptom assessment as an influence on treatment timing and intensity. Of all these, the molecular predictors are fast becoming the single most important in decision-making, in both adjuvant and metastatic settings.

Indeed, it is tempting to predict that today's differences between M_0 and M_1 treatment philosophies will melt away as the efficacy and tolerability of biologically matched drug therapies convince oncologists and their patients to think of cancer as a continuum of chronic diseases rather than as a death sentence. A sophisticated computer-based METS profiling system could give seamless decision-making guidance for all anatomical stages of cancer, like GPS navigations systems in cars (Table 1). For example, in breast cancer:

- an $M_0E_0T_1S_0$ lumpectomy patient might be recommended to receive adjuvant radiotherapy and hormonal therapy;
- an $M_1E_1T_0S_0$ patient could receive an adjuvant course of biological sensitiser together with chemotherapy;
- an $M_1E_2T_1S_1$ patient could receive the same biological sensitiser with chemotherapy as initial therapy, followed by maintenance biological therapy;
- an $M_0E_3T_1S_2$ patient could have remission induction with biochemotherapy, followed by maintenance hormonal and biological therapies;
- an $M_3E_3T_1S_1$ patient may be spared conventional biologicals, and referred instead for a clinical trial of a new biological for which no biomarker is yet available.

Table 1 – Outline of the proposed user-friendly METS profiling algorithm, with hypothetical treatment implications (see text).

Components	Measurables (examples)	Utility	Sub-stage	Definition	Therapeutic implication
M (molecular)	Protein expression	Signifies sensitivity or resistance to specific drugs	0	>2 Sensitivity markers +	Targeted drugs may suffice
	Mutations/cytogenetics		1	1 Sensitivity marker +	Targeted drug +/– local/chemo
	Gene amplification		2	Absent sensitivity markers	Local + chemo
	Gene methylation		3	0 Sensitivity, >1 resistance +	Consider phase 1/2 clinical trial
E (extra-primary)	Skin/muscle invasion	Signifies need for systemic therapy (+/– local ablation)	0	No extra-primary disease	Local treatments may suffice
	Nodal spread		1	Locoregional disease only	Local treatments +/– drugs
	Bone spread		2	Only 1 distant tissue involved	Drug treatment +/– local ablation
	Other visceral		3	Multiple tissues involved	Drug treatment may suffice
T (tumour)	>1 cm invasive	Signifies need for local ablation (+/– drug therapy)	0	No major T risk factors	Adjuvant drugs questionable
	Poor differentiation		1	1 T risk factor	Adjuvant local + targeted drug
	High proliferative rate		2	2 T risk factors	Adjuvant local + chemo
	Diffuse LVI		3	>3 T risk factors	Adjuvant local + target + chemo
S (symptoms)	Silent organ dysfunction	Signifies optimal treatment timing and/or intensity	0	Normal quality of life	Any timing, normal intensity
	Tired, anorexia, weight loss		1	Minor symptoms	Use most tolerable treatment first
	Refractory dyspnoea		2	Major symptoms	Use most effective treatment first
	Refractory pain/cachexia		3	Incapacitated, irreversible	Avoid anticancer treatment

- an $M_3E_3T_2S_3$ patient may reasonably consider the use of palliative treatment alone.

Note that these clinical decisions do not depend primarily on the TNM disease extent, nor do they differ qualitatively between 'adjuvant' and 'metastatic' patients.

3. Conclusion

So: is staging dead? No, but it is fast becoming less important for medical oncologists. This may seem paradoxical at a time when technically impressive staging technologies such as CT-PET are making huge inroads into modern cancer practice, as are newly commercialised prognostic aids such as multigene expression profile kits. The fact remains that these latter advances are unlikely to influence drug sensitivity and patient survival to the same extent as biomarkers such as ER expression, *HER2* amplification, *EGFR/KRAS* mutations, Kit expression, Ki-67 expression and *MGMT* methylation. Yet it is still early days in the biological anticancer story; for though it is exciting to see our former dependence on tumour ablation now being eroded by rational manipulations of the tumour cell genome, the learning curve will be long, expensive and error-prone.

More than any other advance, the development of predictive profiling to guide the use of biologically targeted drugs promises to transform the natural history of hitherto refractory cancer. Fear of surgery, fear of scans, fear of biopsies – all these will come to be replaced by a calmer and more constructive interest in characterising the druggable molecular signature of a patient's disease. This 'medical/chronic disease' paradigm of cancer may seem less heroic than its 'surgical/cure-or-die' predecessor, but the benefits of a molecular approach to decision-making – in terms of patient survival, quality of life and cost-efficacy – should soon prove considerable for malignant diseases of all stages.

Conflict of interest statement

None declared.

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