Has TNM been overtaken by science?

Emma Mason

The biology of a cancer is a key factor determining prognosis and prediction of response. So should we still be characterising it by the size of the tumour and spread of the disease? In a debate at the European Breast Cancer Conference in Nice, a packed hall of delegates was, reportedly, evenly split on the question.

The international system for classifying cancer by tumour size and location, regional lymph node involvement and distant metastases (the TNM staging system) has served oncologists well for more than 50 years. But now questions are being asked about its usefulness in the 21st century. While some people believe that it can and should survive, albeit with some adaptations, others are already writing its obituary.

Chief amongst its critics is Harry Burke, Associate Professor of Biochemistry and Molecular Biology at the George Washington University School of Medicine, Washington DC, USA. In 1993, when he was a consultant to the American Joint Committee on Cancer (AJCC), he proposed that a computer-based system for cancer prognosis should replace TNM. His reasoning was that such a system could include molecular factors, such as oestrogen and progesterone receptor and HER2 status, and it could provide individual patient recurrence and survival predictions for specific therapies. His idea was rejected, but since then he has kept up the pressure with various articles on the subject, and most recently he participated in a debate at the European Breast Cancer Conference 5 (EBCC-5) in March this year, entitled "This house believes that TNM is a waste of time".

The TNM system is a cancer staging classification system that is used around the world as a common language to classify anatomic disease extent in tumours and give indications as to the course of the disease. The French surgeon, Pierre Denoix, developed the TNM Classification of Cancer Stage at the Institut Gustave-Roussy, France, and proposed it to the International Union Against Cancer (UICC), which adopted it in 1953, with the AJCC following suit in 1959.

Since then there has been an explosion in knowledge about cancer. TNM was created before any of the genes implicated in the onset of various cancers had been discovered, before the role of hormones had been revealed, before routine screening had been introduced which enables cancers to be discovered at much earlier stages in their development, and before the introduction of neo-adjuvant and molecular therapies. Biomarkers have been discovered for cancers such as breast and prostate, which enable physicians to have a more detailed view about what treatments would be best for a particular cancer sub-type and the likely course of the disease, yet they are not

"TNM is basically dead... it is clinically misleading rather than informative"

incorporated into TNM and are not predicted by it.

Burke argues that, in an age of increasingly personalised medicine, TNM is unwieldy, outdated and should be replaced by a system that includes tumour size, lymph node status, metastases, and other predictors of outcome, including powerful new biomarkers, in order to provide the most accurate predictions of which therapy would be best for an individual patient. Other oncologists point out that, while TNM may no longer provide all the information that needs to be known about some cancers such as breast and prostate, there are still many cancers where biomarkers have not been discovered or developed, and where cancer staging gives valuable information about not only the extent, but also the likely course of the disease. In addition, they argue that the developed world owes a duty to the developing world to maintain an international classification system that is simple to understand and to use.

Burke told *CancerWorld*: "TNM is basically dead. It cannot take account of the fact that screening is now detecting cancers at much earlier stages when they are smaller; it cannot incorporate new biomarkers; and it cannot incorporate new therapies. So it is clinically misleading rather than informative."

When the TNM system started, all that was known about a cancer was the size of the tumour and the extent of its spread; the existence of clinical symptoms was the only way of detecting it. The system was based on the fact that the larger the tumour and the greater the extent of the spread, the less likely the patient was to survive the disease. TNM organised this spread into 'stages' of the disease, with a higher stage having a poorer prognosis.

However, in October 2004 a paper published in the *Journal of the National Cancer Institute* on colon cancer survival rates revealed that there was an outcome cross-over between stage IIIa and IIb patients, with the IIIa patients, who according to the TNM system should have a worse prognosis, having better survival rates than the IIb patients. The likely reason for this cross-over was that the IIIa patients had received an effective chemotherapy that the IIb patients had not received and this therapy resulted in improved survival – survival that was not taken into account by TNM.

In an accompanying editorial, Burke stated that this proved that TNM was not taking account of new treatments, nor was it taking into account the biology of the disease, and that this was the final nail in the coffin of the TNM staging system.

Burke explained: "The TNM staging system relies on the surgical removal and pathologic description of the anatomic characteristics of the tumour and of any associated lymph node involvement, so that it tells you the prognosis of patients if they receive surgery (whereas some cancers only receive radiation therapy, for example, prostate cancer). Further, what if patients receive other treatments such as chemotherapy or molecular therapy (e.g. Herceptin)? How does it take these factors into account in terms of its prediction of prognosis? It is clear that, today, the staging system is making predictions that are not accurate because other treatments are changing the patient's survival and the staging system doesn't tell you about that. That's a fatal flaw in the TNM staging system."

Supporters of TNM responded to the cross-over in a way that Burke says has shocked many clinicians. "The leaders of the AJCC and UICC, in response to my editorial, wrote that it was all right to have outcome cross-over in the staging system, because it's not a prognostic system,

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it's an anatomic, extent-of-disease system," said Burke. "But once you disconnect prognosis from the staging system, that's the end of the system. Clinicians are totally shocked when I tell them that the staging system is nothing to do with prognosis now." He said most clinicians did not know of the disconnection between stage and outcome and continue using TNM. Yet this approach, using the stages to determine therapy, could mean that some patients were being denied an effective therapy they needed, while others were being treated unnecessarily.

While supporters of TNM say that it is possible to adjust the system so that it can either take account of new developments or can be used to complement prognostic tools such as molecular biomarkers, Burke says that this is impossible because you would end up with hundreds, if not thousands, of different categories that cross over each other, thus defeating the main purpose of TNM – that it is a simple, easy to understand and use, outcome system.

However, Burke feels that the real issue with the use of TNM is what he calls "biological determinism". "The essential question is: are we going to continue to treat our patients based on an anatomic extent-of-disease approach, or are we going to use what we have learned about the biology of the cancer to defeat the tumour that is growing in the patient?"

Seconding Burke at the EBCC-5 debate was Frédérique Penalut-Llorca, a pathologist at the Centre

Harry Burke: TNM is unwieldy, outdated and should be replaced by a system that includes biomarkers and other predictors of outcome

Frédérique Penalut-Llorca: oestrogen and progesterone receptors and HER2 status are all far more relevant than TNM stage in breast cancer

Jean Perrin, Clermont-Ferrand, France. She highlighted the irrelevance of TNM in breast cancer compared with the far more relevant information that is now known about the role of oestrogen and progesterone positive and negative markers (ER and PR), and HER2 status.

"We need prognostic and predictive intrinsic tumour parameters of response to treatment that can be obtained by understanding the tumour biology. These are not in the TNM!" she said.

While not all cancers are as far advanced as breast cancer with the identification and use of biomarkers, Burke says that there needs to be a paradigm shift.

"We need to recognise that cancer is a biological disease and let's base prognosis on the biology of the disease, not on how big it is when it is discovered. If we know about ER, PR, HER2 and p53 status, then we know about the prognosis. And survival is very different, even for patients within the same TNM stage of disease. Your destiny is determined by the biology of your disease. This is the definition of biological determinism."

He believes that a computer-based prognostic system, such as the one that he developed for the AJCC, that can take account of all the patient's biomarkers is still the best way forward, and he has established a model for this at www.cancerhome.com.

Mary Gospodarowicz, Professor

"Clinicians are shocked when I tell them that the staging system is nothing to do with prognosis now"

Mary Gospodarowicz: The TNM system is under continuous review by several expert groups and is able to respond to the challenges of the 21st century

Lars Holmberg: Lymph node status is still the major prognostic divider. Even if another system is developed, we still could not abandon TNM

and Chair at the Department of Radiation Oncology, University of Toronto, Canada, and Medical Director at Princess Margaret Hospital, Toronto, disagrees with Burke and opposed him in the EBCC-5 debate.

She is a member of the UICC Core Committee of the UICC TNM Project, which maintains the TNM classification and has introduced a rigorous process for continuous improvement of the TNM system.

She told *CancerWorld* that nobody was pretending that TNM was a perfect system. "We live in a world that is imperfect. What is important is that we understand the principles of what we are doing, observing and reporting."

The importance of the basic principles of the TNM staging system still remained, she said. "In order to make decisions in cancer you always need to know the anatomic extent of the disease and it always has diagnostic importance. It may be that in selected cancer centres where all the patients have very small tumours (stage I disease), other tumour characteristics are more important than the disease extent for making treatment decisions. But TNM provides a world-wide framework for considering the extent of the disease across all cancer sites."

Although other prognostic markers, such as molecular biomarkers, were constantly being developed, these tools should be used in addition to, not instead of, TNM, she argued. "TNM is useful whether or not you have access to biomarkers. It's not perfect, but it's useful."

The basis for making decisions in cancer rests on several factors:

- the tumour
- the type of cancer (i.e. site, histology, genetic, phenotypic and molecular characteristics) and the extent of the disease (i.e. stage, size, number of lesions, sites of metastasis)
- the patient (i.e. age, race, general health, etc)
- the environment (i.e. what tools and treatments are available for the physician to use, quality of care, and access to appropriate care)

and TNM gives valuable information on several of these. "Everyone in oncology in the world uses the extent of the disease as the main part of their prognostic design," said Gospodarowicz. "Even in breast cancer, if you have a small cancer, with no lymph node involvement and no metastasis, you know that the patient may not need to have chemotherapy or radiotherapy. On the other hand, if the tumour has spread then you know that the patient does need more treatment."

The aims of the TNM staging system, she argued, were to aid the clinician in planning treatment, to give some indication of prognosis, to assist in the evaluation of the results of the treatment, to facilitate the exchange of information between treatment centres and to contribute to the continuing investigation of human cancer.

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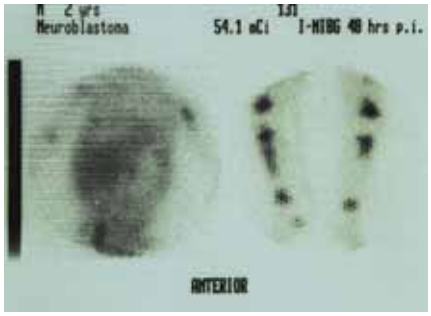

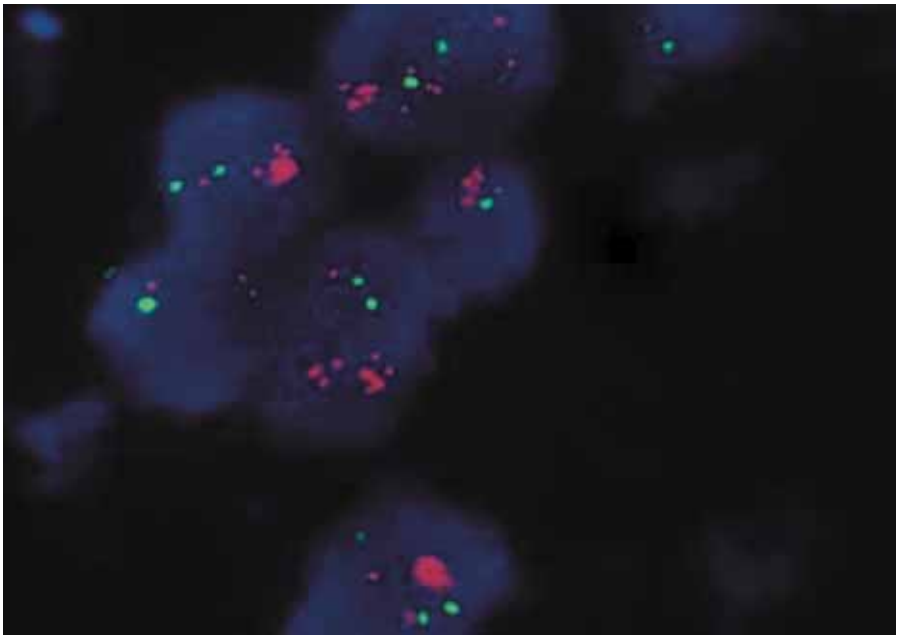

Partial pictures. Proponents of TNM say it is simple, provides vital epidemiological information, and requires relatively low-tech imaging techniques, such as bone scan (*above*). Opponents argue that information on molecular biology, such as HER2 status as revealed by the FISH test (*right*), should be at the heart of any modern staging system

Because TNM had been running as a uniform system for more than 50 years, it was now possible to track changes in cancers over a long period of time, even though some details of staging classification had altered to keep track with developments (Burke disputes this). This, said Gospodarowicz, made it possible to conduct epidemiology studies, investigate the natural history of cancer, and share information from clinical trials.

"Cancer registries need a system that provides a framework for recording and considering all cancers. They need the uniformity provided by TNM," she said.

TNM is subject to a process of continuous review and improvement by several groups of experts around the world. Gospodarowicz believes that this system is capable of responding to the challenges that TNM faces in the 21st century.

"TNM provides a common language for classifying cancer so that people know what they are talking about. There would be total chaos if everyone used different methods for describing different cancers," she said.

Lars Holmberg, Professor of Clinical Cancer Epidemiology at the Regional Oncologic Centre in Uppsala, Sweden, also spoke in favour of TNM at the EBCC-5 debate.

"TNM needs to be maintained for epidemiological cancer surveillance," he told *CancerWorld*. "It is important to know how many people have localised cancer, cancer with regional metastases and cancer with distant metastases. World-wide it has large public health implications. In many parts of the developing world, cancer is becoming the most important disease, once other causes of death such as starvation, infections, malaria and tuberculosis have been dealt with. It's very important to have the TNM system to record and classify the cancer burden here.

"There's the issue of public health planning. TNM is an indicator of the scale of resources that countries will need for cancer treatment, because if you have a large proportion of patients diagnosed when they have distant metastases, that's quite different to people diagnosed with local tumours in terms of the resources needed to treat them.

"TNM is simple and affordable. The developed world has a responsibility to keep the system in operation"

"It is a naïve over-estimation of our progress to believe that traditional staging rapidly will be outdated"

"The developing world will not be able to afford modern, elaborate systems of surveillance of cancer epidemiology and cancer management for a long time to come. TNM is simple and affordable. The developed world has a great responsibility towards developing countries to keep the TNM system in operation."

However, Burke argues that TNM has become extremely complex (for example, the determination of sentinel lymph node involvement) and is itself too complicated for developing countries to use. He mentioned a much simpler system, which predated TNM and is still being used by the US National Cancer Institute, of "local, regional and distant disease spread", and suggested this would be a better system for developing countries to use, especially where patients might not even be able to have surgery.

Holmberg said: "TNM reflects tumour-host balance and tumour burden, none of which is well captured by known biological tumour markers. The cancer burden in one patient is still biologically important and relevant. The surgeon has to know what size a tumour is and whether there is lymph node involvement.

"It is a naïve over-estimation of our progress to believe that traditional staging rapidly will be outdated. Lymph node status is still the major prognostic divider. Even if another system is developed, we still could not abandon TNM."

Although molecular biomarkers are being developed for cancers such as breast, prostate and testicular cancer, there are many other cancers with no known biomarkers as yet. "Breast cancer has been at the forefront for many years in terms of biological markers. But if you look at lung cancer, bowel cancer and gastric cancer for instance, it's more obvious that TNM is still needed," said Holmberg.

While he conceded that there was some validity in the argument that increasingly tumours were being detected earlier, at stage I, and that this consequently affected prognosis, he pointed out that this was far from the norm. "This is a correct argument when we get to the stage where everyone has a small localised tumour, but we are not even there in breast cancer. We still need to know in different countries how many people have what stage of tumour, and there are still many countries, even in Europe, such as Eastern Europe, Turkey, Croatia, where a significant proportion of patients have distant metastases.

"When you look at sophisticated markers that show how a tumour will progress, the actual anatomic burden in one patient at the time of diagnosis is reflecting something of the biology. You need to know the tumour burden to know how much the disease has over-powered the patient, as well as a number of other factors, and TNM reflects this."

Medicine tends to be a conservative field and there is always resistance to change. While this can be good in that it reduces the risk of fads and transient phenomena, it can stand in the way of progress. The crux of the debate at EBCC-5 was: do we determine prognosis and therapy based on the biology of the disease or do we remain with the anatomic extent-of-disease system, perhaps with some adaptations? In the event, the chair, Aron Goldhirsch, declared the vote to be split down the middle. There is no doubt that the debate will continue, which is good for science and for patients.

Further reading, listed by date of publication

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