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Criteria for Prognostic Factors and for an Enhanced Prognostic System

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The American Joint Committee on Cancer proposes the following criteria for evaluating putative prognostic factors: they must be (1) significant, (2) independent, and (3) clinically important. Furthermore, we suggest the criteria for selecting a prognostic system that includes TNM and new prognostic factors. These criteria are: (1) easy for physicians to use; (2) provides predictions for all types of cancer; (3) provides the most accurate relapse and survival predictions at diagnosis and for every year lived for each patient; (4) provides group survival curves, where the grouping can be by any variable including outcome and therapy; (5) accommodates missing data and censored patients and is tolerant of noisy and biased data; (6) makes no a priori assumptions regarding the type of data, the distribution of the variables, or the relationships among the variables; (7) can test putative prognostic factors for significance, independence, and clinical importance; (8) accommodates treatment information in the evaluation of prognostic factors; (9) accommodates new putative prognostic factors without changing the model; (10) accommodates emerging diagnostic techniques; (11) provides information regarding the importance of each predictive variable; and (12) is automatic. ***Cancer*** **1993; 72:3131–5.**

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In this communication, we discuss (1) the adequacy of the current TNM staging system[1,2] in terms of adding new prognostic factors and (2) the criteria that should guide any enhancement of the TNM staging system. Our remarks are illustrated with information regarding breast cancer.

During most of this century, the treatment for breast cancer was either a radical mastectomy, as described by Halsted,[3] or a modified radical mastectomy, as described by Patey.[4] More recently, lumpectomy, chemotherapy, hormonal therapy, and radiation therapy have become important treatment modalities. With the rise of effective therapies has come the need for methods that accurately assess prognosis, because the selection of therapy usually depends on estimated outcome. By the 1950s, there were many incompatible staging systems in use for breast and other cancers.[5] The TNM staging system (tumor, lymph node, metastasis) emerged as a response to the need for an accurate, universal staging system that can be used to determine therapy, select patients for clinical trials, analyze results of clinical trials, and communicate prognosis to patients.[1,2]

Since the TNM staging system began in the 1950s, many new putative prognostic factors have been identified, most within the last 10 years.[6,7] Prognostic factors reported for breast cancer include clinical/epidemiologic/demographic (age[8,9] and race,[10] menopausal status[11]); anatomic (tumor size, nodal status, metastases[12]); and hormonal/cellular/molecular, including receptor status (sex hormone,[13,14] EGF-R[15]), cathepsin D,[16,17] plasminogen activators,[18,19] tumor-related antigens (type 2 carbohydrate[20]), histologic grade[21] and type,[22] proliferative rate (S-phase and DNA ploidy,[23] thymidine labeling[24]), angiogenesis,[25] and genetic information including oncogene amplification (e.g., c-*myc*,[26,27] HER-2/*neu*[28] [c-*erb*B-2[29]]) and suppressor gene loss (e.g., p53,[30,31] and nm23).[32,33]

For the clinician, the past has been a time of few factors and many prognostic systems, followed by few factors and one prognostic system, and currently, a be-

wildering array of factors with no way to test their significance, independence, and clinical importance or to integrate them into a prognostic system. The physician wants to be as accurate as possible when planning treatment but, when confronted with an array of prognostic factors, is often unsure of his or her clinical footing. The physician may therefore be unable to make the best treatment decisions.

We need to integrate the new putative factors into a predictive model to assess whether they add prognostic value and, if they do, to include them in a prognostic system to provide more accurate estimations of recurrence and death.[34,35] It is not possible to integrate new factors into the TNM staging system for several reasons. However, before discussing these reasons, we should define the TNM terminology. "TNM" has three different references. First, there are the primary tumor, regional lymph node, and distant metastasis variables themselves, categorized into tumor size and extent, number of regional lymph nodes containing metastatic tumor, and distant metastases. These are commonly referred to as the "TNM variables." Second, each of these three variables can be combined, that is, specific tumor sizes (Tis, T1, T2, T3, T4), the number of positive regional lymph nodes (N0, N1, N2, N3), and distant metastases (M0, M1) can be grouped together. Each combination of these three variables can be seen as a bin into which patients with these characteristics are placed. This is called the "TNM bin model," and it consists of 40 bins ($5 \times 4 \times 2$).[1] Third, these bins, with one of each of the three TNM variables in each bin, can be grouped according to decreasing survival, to create stages of survival. Taken together, the correlation of stage with survival is called the "TNM stage model." The stages are mutually exclusive and exhaustive; a patient can be in one stage only, and every patient is in a stage.

We now return to the problems with adding variables to the TNM stage model. First, the TNM stage model is based on a bin model and has all the characteristics of a bin model. One characteristic of a bin model is that the number of bins increases rapidly with the number of variables. For example, if we add the variable histologic grade, with its four types, to the TNM stage model, the result is 160 bins ($5 \times 4 \times 2 \times 4$). Thus, for any set of new variables, the number of bins that would have to be added to a stage would be enormous, and the system would become too complex to be useful. Second, adding variables to the TNM stage model would demonstrate another characteristic of the model, namely that it is a post hoc system. In a post hoc system, the outcomes are examined and the bins/stages are arranged in order of decreasing survival. The only way to add a variable to such a system is to collect a large data set with all the predictive variables present and create a new set of stages. With each new variable this process must be repeated. Third, because the accuracy of a bin/stage model depends on the number of patients in each bin, as the number of variables increases the number of bins increases, and the number of patients must increase exponentially to have enough patients per bin to maintain accuracy. Fourth, the TNM stage system is a static system. A characteristic of static systems generally, and the TNM stages specifically, is that the stages must be changed when there is a change in the data underlying the stages. Changes in technology (e.g., imaging) and changes in the pathologic evaluation of tissue (e.g., micrometastasis) have the potential to change the patient population underlying the stages. Discovery of metastases, through improved imaging, and of micrometastasis, by special techniques, may move patients from Stages I, II, and III into Stage IV. This migration creates the possibility that the stages' predictions have changed. Because stages are based on their predictions, a change in the stages' predictions requires a reexamination of the patients in each stage and possibly a change in the stage definitions.[36]

None of the above is meant to suggest that we should eliminate the TNM variables. They are of major prognostic importance and will remain part of any prognostic system. What this does suggest is that if we are to increase our prognostic accuracy, we must integrate the TNM variables with other prognostic variables to create an enhanced prognostic system.

Prognostic Factors

All patient variables are potentially prognostic, but few variables actually have independent prognostic value. Prognostic factor endpoints can include survival, recurrence, and response to therapy. There are many types of prognostic factors. Some factors mark the natural history of the disease. These factors change their prognostic value when the natural history of the disease is altered by therapy, assuming that the therapy is effective or that the patient develops a complication as a result of the therapy (e.g., an infection secondary to the immune suppression resulting from chemotherapy) that changes life expectancy. Some factors are prognostic for certain therapies only, that is, they tell us if the patient has the potential to respond to a particular therapy (e.g., estrogen and progesterone receptors) or to be resistant to therapy (e.g., srp-27[37,38]). Some factors may be prognostic for therapies not yet in existence; they have no current prognostic relevance. Some factors may be time dependent and prognostic only at a certain stage in the disease process. This suggests that some factors that we test at certain follow-up times may not be prognostic at that time, but they cannot be ruled out as future prog-

Table 1. Levels of Prognostic Factors

Time	Factor level	Level characteristics
Intermittent use	Clinical (observation of the patient, also epidemiologic and demographic information)	What we can know about the patient by noninvasive methods.
1905 onward,[39] culminated in TNM stage model in the late 1950s	Anatomic	Extent of disease/time of discovery; what we learn by invasive methods (soon to be supplemented by new imaging modalities). The importance of histology has been known since 1928,[40] but was not added to the TNM staging system.
1970s onward	Hormonal	Characteristics of the tumor, responsiveness to therapy.
1980s onward	Cellular, molecular, genetic	Cellular, molecular, genetic structure and function.

nostic factors. In the TNM model, some factors may be prognostic for certain stages only. Finally, some factors are prognostic only in the context of certain other factors, and some factors are prognostic only in the absence of certain other factors (e.g., a factor may have prognostic value only for patients with lymph node–negative breast cancer).

Prognostic factors can be viewed in terms of four levels (Table 1). Two ideas are immediately apparent. First, as levels of prognostic factors are added, they do not necessarily eliminate previous levels or factors, but rather, new factors can be combined with existing factors to increase prognostic accuracy. Second, these levels interact, for example, young women may have rapid progression of disease possibly due to an aggressive type of tumor. Parallel to these four levels is therapy, that is, the susceptibility of the tumor to the current therapies. Therapy affects each prognostic level. It should be noted that without effective therapies, prognostic information is of little value.

Criteria for Prognostic Factors

According to our criteria, a prognostic factor must be (1) significant, (2) independent, and (3) clinically important. Significant means the prognostic factor rarely occurs by chance. Independent means the prognostic factor retains its prognostic value when new prognostic factors are added. Clinically important means the prognostic factor must be clinically relevant, that is, it can change patient management and thereby change outcome. Meeting these criteria is necessary and sufficient for qualification as a prognostic factor.

Analytic models discover phenomena that meet the assumptions of the model. If, because of the choice of analytic model, only monotonic (i.e., steadily increasing or steadily decreasing) predictive variables are analyzed, then nonmonotonic predictive variables will never be discovered. Thus, even in the initial discovery of putative prognostic factors, it is important that estimators of prognostic significance be selected that work well for most underlying distributions of the variables. Further, the statistical analysis of a putative prognostic factor should be multivariate and include all known prognostic factors. For breast cancer, this includes the TNM variables, histology, and hormonal status. Finally, the laboratory analysis of all hormonal/cellular/molecular/genetic factors must be performed according to standard protocols.[41,42]

Criteria for a Prognostic System

The ultimate goals of any system for cancer outcome prediction should include the following (not in rank order):

1. Is easy for physicians to use. Ideally, it should have input prompts. It should be available on programmable hand-held calculators, microcomputers, and work stations.
2. Provides predictions for all types of cancer.
3. Provides the most accurate relapse and survival predictions at diagnosis and for every year lived for each patient.
4. Provides group survival curves, where the grouping can be by any variable, including outcome and therapy.
5. Accommodates missing data and censored patients and is tolerant of noisy and biased data.
6. Makes no a priori assumptions regarding the type of data, the distribution of the variables, or the relationships among the variables. It should efficiently capture nonmonotonic phenomena and complex interactions among variables.
7. Tests putative prognostic factors for significance, independence, and clinical relevance.
8. Accommodates treatment information in the evaluation of prognostic factors.
9. Accommodates new prognostic factors without changing the model.
10. Accommodates emerging diagnostic techniques: not only molecular tests, but also new imaging mo-

dalities (e.g., endoscopy, computed tomography, and magnetic resonance imaging).[42]

11. Provides information regarding the importance of each predictive variable.
12. Is automatic, that is, the model's output does not depend on the operator. There are three types of nonautomaticity: Type I, preformatting the data; Type II, manipulating the variables in the model; and Type III, manipulating the model itself. We are concerned here with with the latter two types. The model's results should not depend on the skill of the individual who sets the parameters, selects and optimizes the variables, and validates the model. This concept applies primarily to the training and testing phases of a prognostic system. The main problem with nonautomatic models is that it is hard to know how much of their accuracy represents operator skill and how much is operator independent; it is difficult to duplicate operator-dependent model results with different operators. Different operators could optimize different models for different types of cancer, resulting in a different predictive system for every type of cancer and different prognostic factors within a type of cancer. This would take us back to the 1950s, when there were many incompatible prognostic systems. We need to retain the significant advance made by the TNM staging system and remain committed to a single, universal prognostic system for cancer.

The goals of any prognostic system are accuracy and usefulness. The enhanced prognostic system that best meets the above criteria will be more accurate and more useful than the current system. Useful means the ability of the enhanced prognostic system to group patients by any set of prognostic variables for clinical trials and for therapy. The TNM staging system groups patients by a fixed set of variables. The enhanced prognostic system will be more flexible, because it will allow the creation of patient groups by any set of variables. Clinicians will be better able to customize treatment. Researchers will be able to ask more complex questions and create more homogenous patient populations to detect small but important treatment effects.

Conclusion

The TNM staging system has been the mainstay of cancer outcome prediction for many years, and it has been effective in this task. However, to increase our prognostic accuracy, the current system must be enhanced by the creation of a system that contains the TNM variables as well as the new predictive variables. The American Joint Committee on Cancer is using the criteria described above to develop an enhanced prognostic system.

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