Cancer Staging and Grading

Last updated September 25, 2024 17 min read ScholarRx

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Learning Objectives (4)

After completing this brick, you will be able to:

1. Explain what tumor markers are, and describe how they are used to determine prognosis.
2. Define grading, and explain some histologic features used in grading tumors.
3. Define staging, and explain the TNM system of staging tumors.
4. Define prognosis, and explain in general how prognosis is determined for patients with cancer.

disease. Establishing a prognosis is essential for both patients and doctors because it helps each determine the next step of action. Treatments, or lack thereof, depend on the expected course of the disease. If a patient has a terminal prognosis (ie, no chance of surviving the disease) and is only expected to live for a limited amount of time, that knowledge will help them decide how to best spend the remaining time and make plans accordingly.

Why Are There So Many Different Prognostic Parameters?

Different outcome measures are used to determine a prognosis. This can sometimes be very confusing to both patients and students. Survival, for example, can be measured with specific qualifications. Survival rate might be measured at differing end points, such as 5 years or 10 years. Or it might be qualified as cancer-specific, disease-free, or overall:

- **Cancer-specific survival** is the percentage of patients with a specific type and stage of cancer who have not died from that cancer within a certain period of time after their diagnosis. This does not mean that all patients in this group are cancer-free, just that their disease has not resulted in their death from the time of diagnosis until a specified end point.
- **Disease-free survival** is the percentage of patients who have no signs of cancer during a certain period of time after completing their treatment.
- **Overall survival** refers to the percentage of patients with a specific type and stage of cancer who have not died from any cause in a certain period of time after their cancer diagnosis.

Each of these measures is clearly different from the other and each a different way of describing one's prognosis.

What Determines Prognosis?

Many factors are involved in determining a patient's prognosis. The type of cancer is, of course, very important. Some cancers carry a much grimmer prognosis than others. For example, the 5-year overall survival rate for all patients with prostate cancer is 98%; for Hodgkin lymphoma, it is 86%; for colorectal cancer, the rate is 65%; and for lung cancer, the 5-year overall survival rate is only 18%.

STRUCTOR NOTE

There is no need to memorize these percentages at this point - when we get to the specific systems, we will discuss this further

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However, the type of cancer a patient has is only one part of the story. Notice how the term "overall survival" is used above. This means that the stated survival rates are averages for *all* patients with these types of cancer. But within each type of cancer, there is a range of survival, and that range is often huge—with some patients surviving into old age and others surviving less than a few weeks. So once we know what type of cancer a patient has, what factors do we use to establish that particular patient's prognosis?

Stage of the Cancer. Stage defines how large the cancer is and how far it has spread. We will cover this in more detail below. Consider, though, that patients with stage 1 small cell lung cancer have a 5-year survival rate of 31%, while patients with stage 4 disease have only a 2% 5-year survival rate. Staging is generally the most important factor for determining prognosis.

Grade of Cancer. Grade refers to the histologic characteristics of the cancer. We will cover this in more detail later. Suffice it to say that, like stage, the higher the grade of a cancer, the worse its prognosis.

Genetic and Molecular Characteristics. Cancers can have specific molecular characteristics, such as particular gene mutations or cell surface receptors. Specific molecular features can confer a better or worse prognosis. Some molecular characteristics of cancer can make it a target for a specific treatment, which can in turn affect prognosis. Examples include the *BRCA1* and *BRCA2* mutations in breast cancer as well as progesterone receptors, estrogen receptors, and HER2/Neu receptors in breast cancer. Breast cancers that are estrogen-receptor positive carry a better prognosis than those that do not, while cancers that are HER2/Neu negative carry a better prognosis than those that are positive.

Tumor Markers. These are measurable substances that help determine the severity of a cancer and a patient's response to treatment. Examples include prostate-specific antigen (PSA) for prostate cancer and carcinoembryonic antigen for gastrointestinal tumors.

Age. A patient's age and general health are also factors. Elderly patients and immunosuppressed patients (such as those with HIV or diabetes) tend to have a worse prognosis.

Initial Response to Treatment. If a patient responds very well to initial treatment, it might improve their prognosis, while if a patient's cancer doesn't respond to treatment at all, the prognosis is usually worse.

Severity of Certain Signs and Symptoms of Cancer. These are often specific to individual cancers. One example is that patients who become hypercalcemic because of their cancer usually carry a worse prognosis (whether that's because of a paraneoplastic syndrome or because of bone metastasis). The same is true for patients who have cachexia (weakness, anorexia, muscle wasting, and fatigue caused by an illness).

What is generally the most important factor in determining a cancer patient's prognosis?

What Are "Remission" and "Cure?"

In the context of cancer, cure means that there is no trace of cancer whatsoever and the cancer will never come back. When dealing with cancer, it is almost impossible for doctors to be able to make such a statement. We can't be sure that a few undetectable cancer cells no longer

remain.

This is why we so often hear the word “remission” when talking about cancer. **Remission** means that the signs and symptoms of cancer are either reduced or absent. **Partial remission** means that the cancer has responded to treatment and the signs and symptoms are alleviated, but they have not been completely eliminated.

Complete remission means all evidence, signs, and symptoms of cancer have disappeared. Even with complete remission, some undetected cancer cells may remain, and they might cause the cancer to grow back. This is why the word “cure” is seldom used when referring to the treatment of cancer, and it is also why patients with cancer must still be monitored for years after they are declared “cancer free.”

What Is Cancer Staging?

The stage of a cancer is a measure of its size and how far it has spread. It is generally the most important prognostic factor for determining survival. The stage of a cancer has a scale of 0 through 4, and stage is usually determined using the **TNM system**. TNM stands for tumor, node, and metastasis.

Tumor refers to the size of the original tumor. It is quantified from 1-4, with 1 being the smallest and 4 being the largest.

TRUCTOR NOTE

> Sometimes T refers to the extent of local invasion. For Example in a colon adenocarcinoma the T goes from 1 to 4 as the cancer involves the different layers of the wall of the GI tract
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Node describes whether the cancer has invaded nearby lymph nodes. It is quantified from 0-3, with 0 meaning there has been no spread to lymph nodes and 3 referring to spread to many lymph nodes. After metastasis, this is the second most important of these three prognostic factors.

Metastasis describes a cancer’s spread to other organs in the body. It is the most important of these three prognostic factors. It is quantified with either 0 or 1, with 0 referring to no metastasis and 1 referring to metastasis.

The exact anatomical and molecular parameters that determine the specific stage of a cancer can be complex, and they greatly differ from one cancer to the other. A committee of experts establishes the exact criteria for each cancer.

Often, cancer stages will also be written with a number and a letter, such as stage 2A or stage 3B instead of stage 2 or stage 3. The letters are simply a system for further stratifying within stages. Stage 3A cancer carries a worse prognosis than a stage 2B cancer of the same type. For some cancers, there is even stratification within each of the TNM categories, such as T1a and T1b, etc. Describing these is beyond the scope of our lesson.

To illustrate how staging affects prognosis, Table 1 lists the 5-year survival rate as a function of the stage of non–small cell lung cancer.

Table 1

Stage	Five-Year Survival Rate
1A	49%
1B	45%
2A	30%
2B	31%
3A	14%
3B	5%
4, or metastatic	1%

You can see how the stage of cancer can make a significant difference in a patient's prognosis.

:TRUCTOR NOTE

Again, it is not important to memorize these percentages at this time

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What Is Cancer Grading?

The grade of a tumor describes its histologic appearance and the number of mitoses visible in the cells. Cancers can range from well-differentiated, which is low grade, to undifferentiated or anaplastic, which is high grade. Well-differentiated cells bear a close resemblance to the cells of normal tissue, while anaplastic cells exhibit a complete lack of differentiation and do not resemble normal tissue cells at all. Poorly differentiated tumors are usually more aggressive than well-differentiated ones. Although grading is an important prognostic factor, it is not as important as staging.

What is the difference between the stage and grade of a cancer?

A good example of grading is how it is used to describe infiltrating ductal carcinoma, the most common type of invasive breast cancer. Grade 1 tumors are well-differentiated. They have cells that form glands within the breast stroma, and their nuclei are uniform with virtually no evidence of mitotic activity. On the other end of the spectrum, grade 3, poorly differentiated tumors have nests of neoplastic cells with no evidence of gland formation, along with marked nuclear atypia and substantial mitotic activity. Grade 2 is best thought of as the middle ground between these two extremes.

What Are Tumor Markers?

STRUCTOR NOTE

Discussed in Intro to Neoplasia, part 2

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A tumor marker is a compound that can be measured in the serum or urine that is elevated in the presence of cancer. These markers are usually substances that are produced by the tumors, resulting in levels higher than is otherwise normal. Common examples include:

- CA19-9, a marker for pancreatic cancer
- Alpha-fetoprotein (AFP), a marker for hepatocellular carcinoma (HCC)
- Chromogranin, a marker for neuroendocrine tumors
- Prostate-specific antigen (PSA), a marker for prostate cancer
- CA-125, a marker for ovarian cancer

CLINICAL CORRELATION

Prostate cancer is the most common cancer in men, and breast cancer is the most common cancer in women. Lung cancer is the second most common cancer in both men and women, and it is the most common cancer killer in both men and women as well. A better way to state this is to say that lung cancer has the greatest mortality across both men and women, while breast cancer has the greatest morbidity for women and prostate cancer has the greatest morbidity for men.

Tumor markers should not be used as a primary tool for diagnosing or screening for cancer. Levels can vary from patient to patient and can be affected by specific patient characteristics, so they are not a reliable tool for diagnosis. (For example, PSA levels change as men age, so the threshold for elevated PSA levels is different for men of different ages. Therefore, PSA has low sensitivity and specificity for detecting prostate cancer.)

However, after a cancer diagnosis is established, tumor markers can be very useful. A physician can measure the baseline levels of a tumor marker and track the changes over time. A decrease usually signifies a positive response to treatment, while an increase suggests minimal response; this can influence prognosis. Markers can also be used to monitor patients after treatment. Once a patient's baseline level is established after treatment, an increasing tumor marker level later might suggest cancer recurrence.

Remember that PSA stands for **P**rostate-**S**pecific **A**ntigen to recall it is the tumor marker for prostate cancer.

CASE CONNECTION BACK TO INTRODUCTION

Thinking back to PF, how do you explain the summary to him? What is his prognosis?

You explain to PF that the abbreviation is a way of reporting the staging of his lung cancer. Staging describes the size of the tumor (T), whether or not it has spread to the lymph nodes (N), and whether there is distant spread of the cancer or metastases (M). You explain that his tumor is between 4 and 5 cm in size, and there is no spread to either the lymph nodes or distant sites. "With this information, we can give you some numbers about your prognosis. Your 5-year survival is 31%," you tell him.

Summary

- Prognosis is a forecast of the likely course and outcome of a patient's disease. Having a prognosis helps inform patients and providers on the best steps in management.
- Numerous outcome measures are used when giving a prognosis. Because each type of cancer has a range of possible prognoses, each patient must be individually evaluated to determine an accurate prognosis.
- There are many factors involved in determining the prognosis for a patient with a particular type of cancer (eg, lung or breast cancer). In general, the most important of these is the stage of the cancer (eg, stage 2 or stage 4).
- Cancer staging describes the size and spread of a tumor. We use the TNM system to establish the stage of a cancer. M refers to the distant metastasis of cancer, and it is the most important prognostic factor; lymph node involvement (N) is the second most important.
- The higher the cancer stage, the worse the prognosis.
- The grade of a cancer describes its histologic features.
- Grading also contributes to prognosis, with a high grade conferring a worse prognosis. However, grading is not as important a factor as staging.
- Tumor markers are measurable compounds that are useful for measuring response to cancer treatment, prognosis, or the recurrence of disease. They are generally not useful for diagnosis.

Review Questions

1. Which of the following patients carries the worst prognosis?

A. A 25-year-old man with stage 3 Hodgkin lymphoma

B. A 50-year-old man with stage 2 colon cancer

C. A 65-year-old woman with stage 3 estrogen receptor–positive breast cancer

D. A 70-year-old man with stage 4 lung cancer

E. A 75-year-old woman with stage 3 lung cancer