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**COMPLEMENTARY /
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In the Know

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October 2004

from

The Duke Patient/Family Resource Center

The Duke Patient/Family Resource Center is:

- A lending library offering books, audio and video tapes, magazines and free brochures dealing with cancer and certain blood disorders and with issues of coping, survivorship, caregiving, and grieving
- Open 8:30 to 5:00 every day the Morris Clinics are open
- Located in the White Zone, first floor, of the Morris Cancer Clinic, Room 15123.
- Our phone number is 919-684-6955. Our email address is FamilyLibrary@mc.duke.edu

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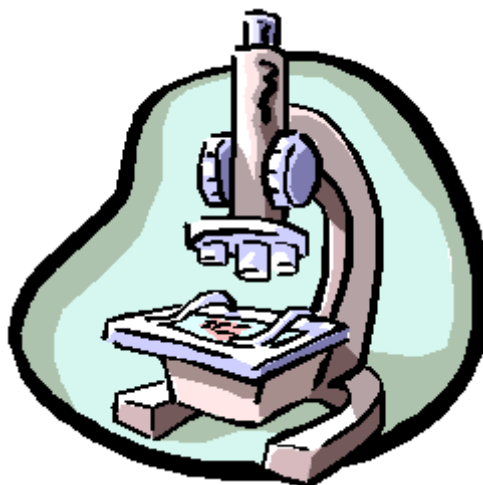
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Your Pathology Report



The first step in the diagnosis of a cancer is very often a pathology report, or a "biopsy report," based on a small sample of tissue removed from the patient's body. Very often this sample is removed by "fine needle aspiration" and is essentially a thread of cells. If this small sample, the biopsy, is positive for cancer, doctors will set about determining, in as great detail as possible, the kind of cancer present and how far it has progressed. These two pieces of information jointly yield an understanding of your prognosis and the best treatment options.

Pathology reports continue to play a large role as the investigation proceeds. If surgery is the next step, the surgeon in certain instances will have a pathologist by his side to perform a quick "frozen section" scrutiny of a larger piece of the tumor. This is a check against the biopsy report. Removal of an organ or body part is often at stake and will not proceed if the frozen section contradicts the original biopsy.

Finally, at the end of a tumor-removing or tumor-reducing round of surgery, all samples of tumor, lymph nodes, and associated items are sent to pathology for a more comprehensive report, which, combined with scans, x-rays and blood tests, furnish the medical team with a fuller understanding of what sort of situation they are dealing with. For some cancers, tiny tell-tale details, hard to detect without state of the art technology and seasoned judgment, are critical to diagnosis, treatment choice or both. One reason that people come to highly regarded cancer centers, like Duke, is to feel

assured that this kind of information is accurately assessed and its implications understood.

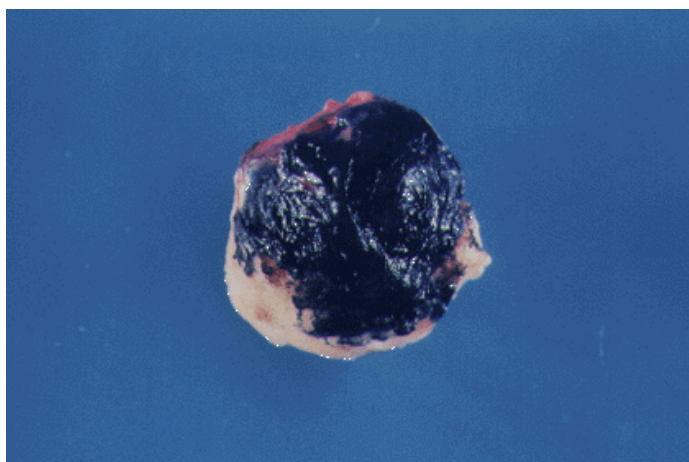
In this issue of *In the Know*, I will try to give you a more intimate view of the pathology report and its significance. In what follows, I am greatly indebted to three pathologists from the Duke Department of Pathology. They are Dr. Anand S. Lagoo, Director, Flow Cytometry Lab ; Dr. John F. Madden, Associate Professor, Dept. of Pathology, and Dr. Rex Bentley, Associate Professor, Pathology Clinical Services.

The Role of Pathology in Assessing a Cancer

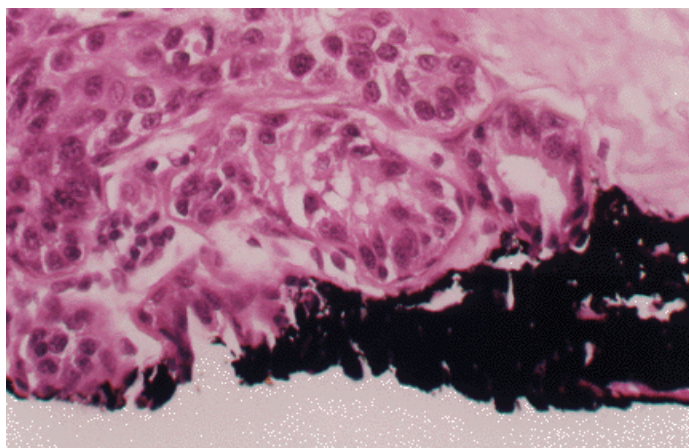
Doctors will want to know not only what kind of cancer is present but how far it has progressed. "Kind" and "stage" are the two big questions. Pathology enters into both.

Staging. Determining how far a cancer has progressed is called "staging," and your cancer will eventually be assigned a "stage." With solid tumors, the usual formulation is a four stage system. The lowest stage, Stage I, is a cancer that has only just begun to invade surrounding tissue and has not yet started to leak cells or seed out to other parts of the body. On the other end of the spectrum, a Stage IV cancer is one that has spread, or "metastasized" to at least one distant site from the original tumor. (For some cancers there is a Stage V, for some cancers there are substages, like IIIa, b, c etc. A few cancers have only the simple dichotomy "local" vs. "advanced.") Staging typically involves scanning the body in various ways – X-rays, MRIs, P.E.T. Scans - and putting these results together with more direct examinations of the tumor tissue.

Pathology and staging. Because surgical excision of all or part of any solid tumor is typically a part of "staging," the final decision as to how advanced a cancer is often comes from examining what the surgeon has removed. This is one of the pathologist's many jobs. He/she will perform careful measurements on the excised tumor or tumors, and will check for "positive margins" on the excised material. If a tumor has been completely excised, it will be encased in a margin of normal tissue. Should the pathologist find even one cross-sectional slide in which cancer cells come all the way out to the outside of the lump, the margins are said to be "positive" for cancer and the surgeon will have to go back in (if that is possible).



The excised lump is first painted, then slides are made from cross-sections.



If a cross-section shows tumor extending to the paint, as above, the lump is said to have positive margins.

With solid tumors, the surgeon will usually remove a collection of the lymph nodes nearest to the area where the tumor resided. These too are sent to the pathologist. Should cancer cells from the tumor be found in any of them, this is an indication that the cancer has begun to leak out into the body. It may not be at Stage IV, but it is no longer at Stage I. For abdominal or chest cancers that protrude outside their organ of origin, patches of tissue from adjacent areas are also sampled for cancer cells. Once again, if even a tiny number of cancer cells appear in these adjacent areas, the cancer has progressed beyond Stage I. For many cancers, progression beyond Stage I means that the patient will have to receive adjuvant chemotherapy in addition to the surgery.

Grading, typing, and probing those molecules. In addition to contributing information related to the stage of a cancer, the pathologist has the job of determining what “kind” of cancer is involved. In examining the specimens of tissue, blood, bone marrow or fluids taken from the patient’s body, he/she will itemize

the sorts of cells present, the sorts of tissues these cells compose, and certain key features of the cells and tissues. Sometimes, he/she must produce an estimate of the number of a certain type of cell present in a given size sample. The pathologist is asking a number of questions. He/she is asking about the origin of the cancer, the grade of the cancer, the cell type of the cancer, and whether it has genetic or molecular features known to be relevant to final diagnosis, prognosis or treatment.

Origin of the cancer: The first and most obvious question is from what tissue or organ did this specimen of cancer originate? Not as simple as it sounds. A specimen of cancer taken out of the lung, for instance, need not be Lung Cancer. It might be a metastatic cancer coming from somewhere else like from the breast or the colon. If it comes from the breast, say, and not the lung, it must be given the treatments prescribed for metastatic Breast Cancer, not Lung Cancer. The lungs, the liver, the bone and the brain are the favorite sites for distant metastases, so specimens taken from any of these four areas must be examined with metastasis in mind. The pathologist will be able to tell, under the microscope, whether these cancer cells are lung cells, or metastatic cells from elsewhere now residing in the lung.

If cells are foreign to the organ hosting them, often the pathologist will be able to discern, from microscopic features, their organ of origin. In those less common cases where the cancerous transformation has distorted the cells beyond visual recognition, there are other tests that can be performed to figure out their origin. In a tiny minority of cases, the origin of a metastasis is never pinned down.



Pathologists at work

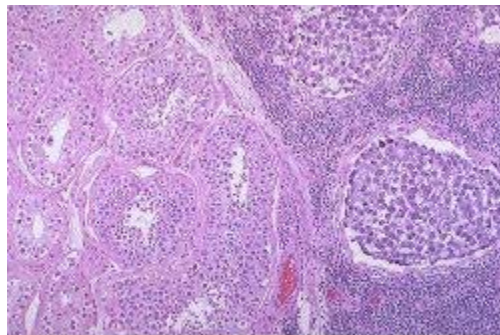
Grade of the cancer. Another commonly asked question is how much distortion has the cancer attained? How far are the cells

removed, in appearance, from normal cells? Often the concept of “differentiation” is invoked here. A normal cell is a mature-looking, perfectly differentiated cell; its components are in the right number, the right proportion and in the right relationship to each other. Furthermore, the tissue that the cell composes is orderly and properly structured for that kind of tissue.



Normal Testicular Tissue

With cancer, distortion begins to creep in. The cells become less differentiated. They are often larger, mis-formed, with some parts disproportionately large; they may have more of a certain component than usual, including more chromosomes in their nuclear DNA. Their shape, and the shape of their parts, is more irregular. As cancer cells evolve toward a more “undifferentiated” appearance, the tissue that the cancer cells compose, the “tumor,” becomes progressively more disorderly until it takes on the appearance of just a chaotic pile of cells.



Normal Tissue adjacent to Seminoma

Determining the degree of differentiation of cancer cells is called “grading” the cancer, and the reason this information is important is that less differentiated cancers are more aggressive cancers and require more aggressive and prompt treatment. Each cancer – lung, prostate, breast, etc. – has its own special grading system, worked out in light of thousands of past cases. Whatever the particulars, all grading systems progress from low numbers (not very aggressive) to high numbers (very aggressive). I will discuss one grading system, the Gleason Scale for prostate cancer, below.

Rate of division. Pathologist may also conduct tests on samples of cancer cells to see how rapidly they are dividing. The more rapidly dividing, the more aggressive a cancer is considered to be. Usually the two measures of aggressiveness correlate, the rapidly dividing cells are usually also higher grade and vice-versa.

Cell types. Within each general category of cancer – lung, lymphoma, prostate, kidney, ovarian, etc. – there are recognized subtypes usually based on the distinctive type of cell that started the cancer. Any given organ – kidney, ovary, skin, the lymphatic system – is composed of different cell types, any of which might provide a starting point for cancer. Some starting points are worse than others. This may be because the cancer produced from that cell type is more aggressive, or because it is resistant to treatment, or both. In ovarian cancer, the “clear cell” type is known to be more chemo-resistant. In kidney cancer, the “transitional cell” type is known to be highly curable, while the “renal cell” type is more aggressive and treatment resistant.

In some cancers, such as breast cancer, there are, in addition to cell types, special subtypes based on distinctive appearances that the cancer cells may assume, for unknown reasons, even though their starting points are all “ductal cells.” The ductal breast cancers with certain appearance-labels like “medullary” or “tubular” tend, for whatever reason, to be less aggressive.

Genetic and molecular characteristics. At the molecular level, cancer cells are treasure troves of information that might be useful in diagnosing and destroying them. As molecular genetic science advances, more and more is being learned about the common genetic mutations found in cancer cells, the types of proteins these cells produce as a result of their altered genes and the types of protein receptors that appear in the cell nucleus or on the cell surface. With this knowledge, medical science can interfere with a cancer cell at the molecular level, using targeted drugs. It pays, then, to know key tidbits about the molecular characteristics of one’s cancer cells.

Finding out these tidbits is another task that has devolved to the pathologist. Breast cancer samples are now routinely tested for whether the cells show receptors for the hormones, estrogen and progesterone, both of which act as a growth stimulant. If so, hormone blocking drugs such as tamoxifen (Novaldex®) or anastrozole (Arimidex®) can nowadays be used to starve the cells of their hormone supply. Breast samples are also tested for whether the cancer cells are genetically mutated so as to over-express Her2/neu, a growth stimulating protein. If so, the drug trastuzumab (Herceptin®) can be used to block the Her2/neu receptors and shut down this form of growth stimulation.

Another reason for probing cancer cells at the molecular level is that in some cancers, it may not be clear what cell type the cancer is, or what grade, until the cells have been tested for the presence of certain proteins. The various leukemia and lymphoma subtypes often require molecular probing before a definitive diagnosis can be given. An example appears below.

The Significance of the Pathology Report

Reading your path report. Patients have a right to view their medical records if they so desire and some of you might want to read your path report. Ask your doctor for a copy. To get an idea of how a path report is laid out and what sort of language it involves, I recommend the following website.

<http://www.cancerguide.org/pathology.html>

Scroll down to "Pathological Examination" for the main highlights.

In most cases, it is less important to be able to master the terminology of path reports and read them yourself, than to appreciate how much can be riding on the pathologist's judgment. Taking the same slides and samples to a second pathologist for a second opinion is an option that patients should not shy away from if there is any ambiguity. Many of the published guides to getting through breast cancer or prostate cancer, for instance, recommend a second opinion as a routine necessity. In both of these types of cancer, and undoubtedly in many other cancer types, there are tricky situations that might trip up a pathologist with insufficient training or experience. In a third cancer type, lymphoma, there are subtypes that look astonishingly alike under the microscope but behave astonishingly differently in the human body. I will concentrate here on breast cancer, prostate cancer, and these lymphomas, to get my point across.

Tricky situations with breast biopsies. In cases where the patient's breast lump turns out to be benign, Dr. Susan Love explains on p. 162 of *Dr. Susan Love's Breast Book*, some pathologists simply "cut to the chase" and give a diagnosis of "fibrocystic change" to account for the lumpiness. Says Love,

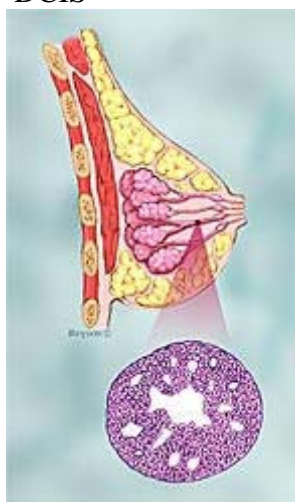
That's not an adequate diagnosis. If your report says that, you should ask for a more specific diagnosis, even if it means making the pathologist go back, look at the slides again, and describe exactly what's there. Under the rubric of "fibrocystic disease" there is one entity that does increase your risk of subsequent breast cancer: atypical hyperplasia. You want to know if that's what you have.

Usually pathologists do note the various forms of pre-cancerous

distortion that show up in a biopsy, but as Love points out, it doesn't hurt to be doubly sure. A woman who knows that her "fibrocystic change" involves atypical hyperplasia might, minimally, want to arrange for more frequent follow-up observation.

Then there is the issue of breast "calcifications" that show up on the mammogram. Calcifications sometimes indicate that a common form of pre-cancer, "ductal carcinoma in situ" (DCIS) is present. When DCIS is present, a woman is at elevated risk for the real thing - invasive carcinoma - and the real thing is most apt to first make its appearance in an area where there is DCIS. Thus it makes sense to biopsy the tissues containing clusters of calcification and see just what kind of cells are lurking in that area.

DCIS



Invasive cancer



Images from breastcancer.org, a nonprofit organization dedicated to providing the most complete, reliable and up-to-date information about breast cancer.

Unfortunately, the biopsy needles (there are usually five) may shoot right past the calcifications and fail to pick up any for the pathologist to examine. If the mammogram showed calcifications and the path report comes back with NO MENTION of calcifications, a crucial part of the diagnosis has been omitted. A sample containing the calcifications must be obtained and examined.

Nowadays, breast pathologists face a new challenge, according to Dr. Bentley, that of trying for a definitive diagnosis on the basis of just those tiny fragments of tissue extracted by the needles, rather than waiting until an entire "lump" is at their disposal. This is because there is a new trend toward giving women "neoadjuvant chemotherapy" - which is chemo prior to rather than after the surgery. The advantage of this is one gets to see, from the response of the breast tumor, whether the chemo is having any effect. (It will be switched if it is not). And, if all goes well, the surgeon now deals

with a shrunken tumor and can spare more of the breast. However, the burden is now on the pathologist to determine on the basis of sometimes barely adequate evidence the variety, grade, and molecular characteristics of the tumor.

Tricky situations with prostate biopsies. With prostate examinations, the biopsy needles (and there are usually six) can also miss the cancer. Or, occasionally, a needle may catch an area that is certainly worrisome to the pathologist but not entirely diagnostic for cancer. In this event, follow-up biopsies may be advisable. Finally, there's the tricky job of grading the samples of cancerous prostate tissue that the needles do catch.

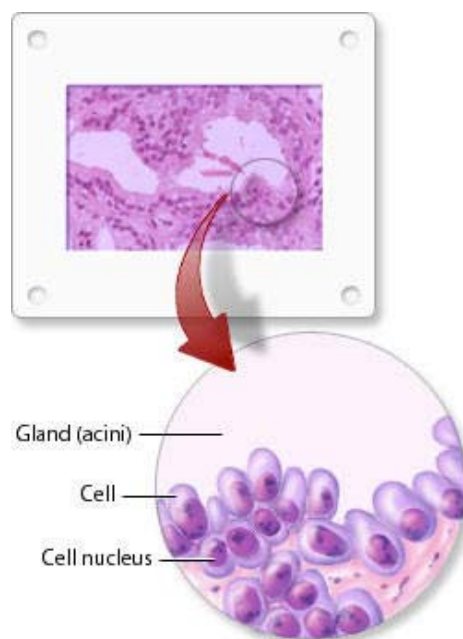
As many of you have undoubtedly heard, prostate cancer presents a very wide spectrum of seriousness, ranging from relatively indolent cancers that can be simply "watched" for years with follow up appointments, to highly aggressive ones that warrant prompt, aggressive treatment. If the cancer is caught early but looks aggressive, the patient is on the cusp of a tough decision. The doctor may well urge a radical prostatectomy, which incurs a distinct risk of subsequent impotence or incontinence, or both. Here is a situation where one really wants to know, beyond any doubt, whether the pathologist got it right!

Turn now to the pathologist. He or she will be undertaking what has come to be called the Gleason Grade, from the doctor (Donald F. Gleason) who devised it. The starting point of Gleason's research was the observation that the prostate tumor typically comes with a gradient of tissue that ranges from almost normal, with the well-formed tubular structures that are characteristic of healthy prostate tissue (white patches below), to highly deformed, with either defective tubules or none at all. Composing each type of tissue is a corresponding cancerous cell - a well differentiated cell for the almost normal tissue, poorly formed cells for the poorly formed intermediate tissues, and undifferentiated cells for the very abnormal tissues.

Gleason was able to single out 5 such characteristic patterns, ranging from least deformed (1) to most (5). He then found that summing the scores of the two most common cell patterns in a tumor (or in a sample of a tumor, i.e. the biopsy) produced a pretty good predictor of tumor aggressiveness. This summing is now called the Gleason Grade, Gleason Score, or just Gleason.

The lowest possible Gleason Grade is 2, the highest 10. The most common score is 6, which represents a cancer that is likely to be moderately aggressive. Scores of 9 or 10, less common, represent the most aggressive end of the Gleason spectrum.

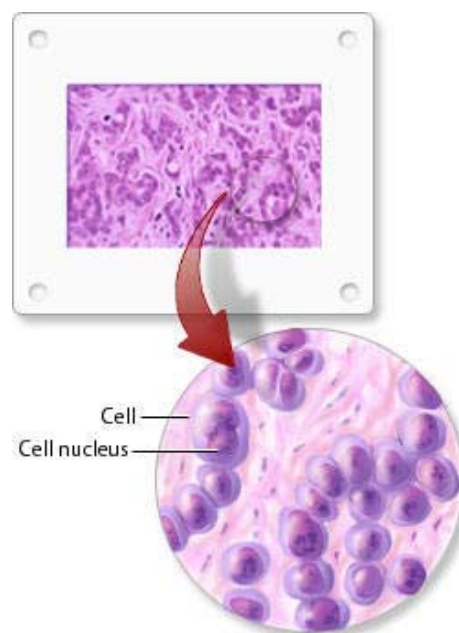
Low-grade prostate cancer



Illustrations by Jodie Jenkinson, © Copyright
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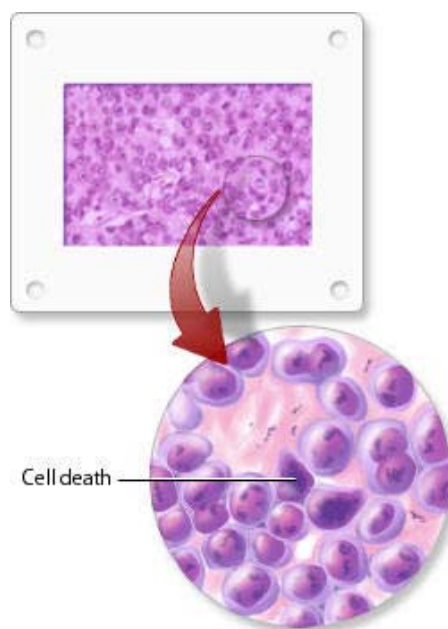
All pathologists now must master the five patterns. All must also master the harder part which is deciding which pattern is the most common and which is the next most common. (This gets much harder if you haven't quite mastered the five patterns.) Say the greatest percentage of the tumor tissue is composed of grade 3 cells, and the next greatest percentage of grade 2 cells. The patient will be said to have a "Gleason" of 5. What if the pathologist is off by one point? While many factors besides the Gleason are weighed in prostate treatment decisions - the man's age and expected life-span, his other health conditions, etc. - for a given man, the Gleason may tip the balance toward or against a particular treatment choice. The difference between a Gleason of 5 and a Gleason of 6 might be the difference between not being sent for a radical prostatectomy and being sent for one. The difference between a Gleason 5 and a Gleason 4 might be the difference between providing appropriate treatment or sending the man home lulled into complacency about a worrisome cancer.

Medium grade prostate cancer



The Gleason Grade, as you can see, represents both a classification of types and an estimate of proportion. So there are two dimensions of subjectivity involved here. Surveys have been done around the country to see how well the pathologist's Gleason on the biopsy matches the final Gleason after the tumor has been removed and examined more fully. The findings are that pathologists at major teaching institutions usually get it right. Here at Duke, on difficult cases, the pathologist will automatically seek a second opinion; and Duke is perfectly willing to have a case sent to an outside expert if the patient so wishes. Dr. John Madden assures me that Duke always reviews prostate biopsies coming in from elsewhere and the Duke pathologists have, as a rule, found the quality of diagnoses rendered at other North Carolina institutions quite high.

High grade prostate cancer



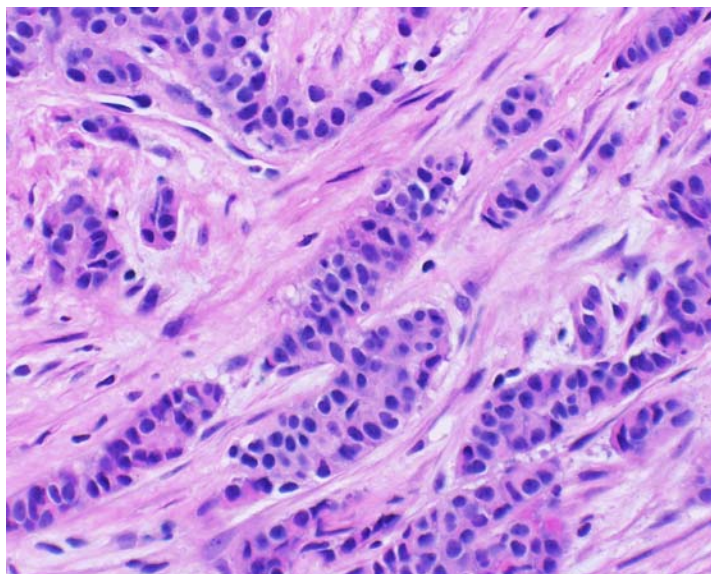
"Look-alike" lymphomas. First a word of clarification about what a lymphoma is. The body has a lymphatic system - a network of channels and "nodes" that circulates lymph throughout the body. Lymph is a clear fluid that carries our white cells, the cells that seek out foreign pathogens and organize an immune response (e.g. inflammation, fever) against them. Lymph nodes act as little filters or traps that sequester foreign pathogens and *abnormal cells* giving the white cells a chance to process these and organize their response.

Because of their ability to trap abnormal cells, lymph nodes often become the first detectable repositories of a spreading cancer. That is why when a new cancer is being surgically removed, surgeons dissect out - and send to pathology - a certain number of the nearby lymph nodes to determine whether the tumor has begun to leak.

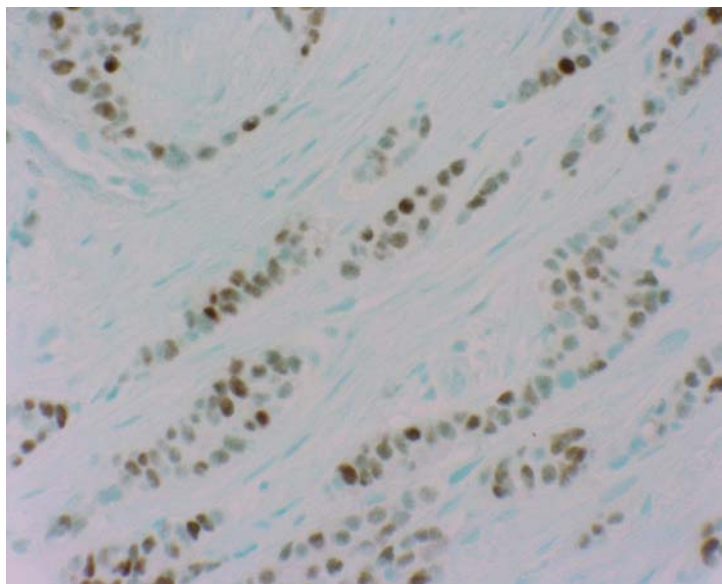
But to be told that you have cancer in one or several lymph nodes is not the same thing as being told you have lymphoma. Lymphoma is a cancer type in its own right, one that has as its starting point one of your white cells. It too can clog your lymph nodes, but that is not the key to the lymphoma diagnosis. The pathological analysis of the cells is what is crucial. The variety of types of lymphomas is impressive - 31 if you include the very distinctive Hodgkin's Lymphoma - and some of them are hard to tell apart. Here the pathologist has a special task.

An example, pointed out by Dr. Lagoo, is Small Lymphocytic Lymphoma and Mantle Cell Lymphoma. Too similar to tell apart under the microscope, they nonetheless follow very different patterns of progression. A person with Small Lymphocytic Lymphoma could live, untreated, for as long as 20 years. A person with Mantle Cell would die within two years if left untreated. It

used to be that these two lymphomas were not distinguished and this cancer acquired a reputation for treacherousness. But one of the tricks of the pathologists' trade is the staining of slides to bring out different features of the cells and tissues being examined. As an example, here are two slides of breast cancer tissue, one with the usual stain, and the other with a special stain designed to test for estrogen positivity.



Slide 1: Invasive ductal adenocarcinoma of the breast, usual stain.



Slide 2: Same tissue as above, stained to bring out estrogen receptors.

Slides courtesy of Dr. Rex Bentley, Duke Dept. of Pathology.

A few years back, a new stain (sorry, no pictures) was developed to reveal the presence of the protein Cyclin D1, which is over-expressed in some cancers. Bingo! This stain revealed that about 20% of the so-called Small Lymphocytic Lymphomas over-expressed Cyclin D1. These turned out to be the aggressive

cancers, and a new category for them, Mantle Cell Lymphoma, came into being. Now, staining for Cyclin D1 is a routine operation whenever lymphoma cells resemble Small Lymphocytic Lymphoma.

Summarizing. Examples could be multiplied, but I think the point is clear. Your pathologist, hidden away as he or she usually is in the bowels of the clinics, and present to you only as a signature on the bottom of a report, is a critical member of your medical team. Taking the time to learn what he or she was looking for and what he or she found in your biopsy and surgical samples will clarify the treatment options that are being presented to you and allow you to raise appropriate questions.

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