What Is Meant by Cancer?

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What is cancer and what is a malignant cell? Is it something that has already spread to other organs or something which has the potential or capacity to spread? This note is an analysis of the issues associated with diagnosis of pre-cancerous lesions including carcinoma in situ. The intent is to examine the broad set of diagnosis of these types and whether they merit the description of being a carcinoma. This issue has become more relevant as we have seen increasing diagnosis of "cancers" and many of them being early stage confined cellular lesions. We fundamentally ask the question: is here a bright line between abnormal growth and cancers? Unlike many of our other notes this one poses a multiplicity of questions which may beg for answers.

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1 INTRODUCTION

What is cancer and what is a malignant cell? Is it something that has already spread to other organs or something which has the potential or capacity to spread? This note is an analysis of the issues associated with diagnosis of pre-cancerous lesions including carcinoma in situ. The intent is to examine the broad set of diagnosis of these types and whether they merit the description of being a carcinoma. This issue has become more relevant as we have seen increasing diagnosis of "cancers" and many of them being early stage confined cellular lesions. We fundamentally ask the question: is here a bright line between abnormal growth and cancers? Unlike many of our other notes this one poses a multiplicity of questions which may beg for answers. As usual, any and all comments are welcome.

Before addressing the full question let us first address the meaning of capacity or potential. The reason for doing so is to better understand what we mean by "carcinoma in situ" or that the cells are cancerous but they are not malignant to the extent that they are moving about, only that their local presence looks ominous. We see this construct in many cases such as the prostate, the breast, the thyroid and the skin. Namely, when the cells take on certain characteristics which we perceive as a potentially malignant process, yet not quite there. Thus, a great deal rests upon our understanding of potential or capacity to do something.

Our focus herein is with what is called "carcinoma in situ" or CIS. As we shall note later, CIS has the characteristic of having the "capacity" or "potential" to become a full-blown cancer, including metastatic growth. The fundamental question is; what do we mean by capacity or potential? Does a pigeon have the potential to become an eagle? No. Does a pigeon egg have the potential to become a pigeon that can fly? Yes, possibly. Thus, capacity or potential is a statement that is not deductive but rather inductive. Can we say a HGPIN in the prostate will inevitably become a metastatic carcinoma? No. In fact we know that HGPINs may actually disappear and never become anything at all. Thus, our first challenge is to address the meaning of capacity or potential. This may be a bit afield for a paper on cancer, but for a patient, hearing the word "cancer" can evoke all sorts of negative effects.

Let us start with Aristotle and his handling of the concept of capacity or potential in his work, *The Metaphysics*[1]:

Potentialities as a whole we can divide into:

the in-born, such as the senses,
the acquired by practice, such as that for flute-playing, and
the acquired by learning, such as that for skills.

[1] Aristotle. The Metaphysics (Penguin Classics) (pp. 263-264). Penguin Books Ltd. Kindle Edition.

The last two of these groups are to be had on the basis of previous actualization, the potentialities, that is, that are conditioned by habituation and the grasp of an account. But such previous actualization is not required for those potentialities which, not of this kind, are conditioned merely by the bearer's undergoing a certain affection.

Although Aristotle is here describing human potential it is not difficult to expand this to cells. For a cell to have the potentiality to be cancerous is can be divided into:

i. the genetic in-born, namely the cell has an innate genetic makeup that predisposes it
ii. the acquired by mutation, such as what we would find in irradiated cells or cells resulting from reactive oxygen species interference
iii. the acquired my environment, such as would be the case where the cell receives signalling or epigenetic changes that incite cancerous changes

Aristotle continues[2]:

Potentiality (is defined as):

(i) The principle of process and change, either in another thing or in the same thing qua other. The art, for instance, of building is not present in what is built, whereas with the art of medicine, it may, since it is a Capacity, be present in the person being healed, but not qua a person being healed. So, what is a principle of change or process in this way is said to be a Capacity, whether in something else or in the thing itself qua something else.

(ii) Also, a principle of change or process through the agency of something else or of the thing itself qua something else. After all, it is by dint of the principle by which something affected is affected in some way that we say that the thing affected has a Capacity for being affected, and this sometimes merely if it is affected at all, sometimes not with regard to its each and every affection but only if it is affected for the better.

(iii) The Capacity for performing the given function well or in an intentionally guided manner. For instance, on occasion one says of those who can just about walk or talk but not do so well that they do not have the Capacity to talk or walk. …

Given that there is this plurality of accounts of Capacity, in one way the account of the potential will correspondingly be of something that has a principle of process and change (given that what can induce stasis is also a sort of potential) in something else or in the same thing qua something else.

Aristotle has laid out three meanings. Note the first, wherein he argues that the "art of medicine" may be included in the "person being healed". There is a nexus between the art and the person but not qua the person. This first definition tris to have a clear continuum between cause and

[2] Aristotle. The Metaphysics (Penguin Classics) (p. 131). Penguin Books Ltd. Kindle Edition.

effect. The second definition is via a separate agency this allowing the cause and effect to be separate from one another unlike the art of medicine and the involvement of the patient. The third is a bit obscure in that it relates to the potential but of something which cannot fully carry out the desired effects. Perhaps here we can have a CIS? He continues;

Another account has it that a thing is potential if something else has a Capacity of … over it, and another is that it is potential if it has the Capacity to change into something of whatever sort, whether for worse or for better. Indeed, even what is destroyed is held to be potentially destructible, since it would not have been destroyed if it had no potential for it. In fact, however, what is destroyed has a certain disposition, a cause and principle of an affection of this sort, this being held sometimes because it is thought to have some state and sometimes because it is thought to have been deprived of it.

If, then, a privation is in a way a state, then everything would be deemed to be potential, potential by dint of having a certain state, and, if not, then by homonymy, with the result that things are potential both by dint of having a certain state and a principle and by having the privation of this – assuming one can be said to have a privation. Yet another account is that something is potential by dint of the fact that neither any other thing nor itself qua other thing has a Capacity to destroy it. Now, also all these cases are examples of Capacity either by dint of the fact that the event in question might or might not turn out to happen or by dint of the fact that it might do so either well or badly...

He then poses the issue of the contrary to potential as follows:

*As for **non-potentiality and incapacity**, this is the corresponding privation to this kind of potentiality, and so every potentiality is of the same thing under the same aspect as the corresponding non-potentiality. There are, though, a plurality of accounts of privation, as follows:*

(i) that which does not have f;

(ii) that whose nature is to have f, if it does not in fact have f (either at all or at a time when it would be natural for it to have f, and either in a particular way, as, say, completely or to some extent or other);

(iii) in some cases, things constituted to have f and lacking it through force, are said to be deprived.

Thus incapacity is more simply based upon; (i) not having the necessary fundamental elements by its very nature to accomplish the task, a dog with no wings, (ii) being fundamentally of the nature to fly but not having the essential element to accomplish it, such as a bird born with no wings, (iii) an entity being fundamentally of its nature but having been exogenously deprived of them, a bird whose wings were cut off. How then does this apply to CIS. In case (i) we would argue that the cells by their nature, genetic etc. makeup, are unable to metastasize, in (ii) the cells may possess the genetic faults but they are blocked by other similar faults, and (iii) the cells may possess the genetic faults but some factor such as an epigenetic blockage prevents it from operating.

This is a long but essential discussion. If we assert some form of capacity or potentiality, we must be asserting it on one of two bases. First, there is in the cells an inherent and identifiable set well defined and determined elements, which is activated as they would be in the natural course of the cell's life, lead to a cancer as we understand that to be. Namely, we can identify and assert a causality. If the genes or whatever in the cells are in some state X, we know that state X inevitably goes to state Y. This is the deductive approach. Second, on the other hand, we can assert that by multiple observations we have a fairly his probability that if we see cells in state X that they may most likely become cells in state Y. This is the inductive approach.

Just where are we today? Unfortunately, we do not have the genetic or similar certainty that X becomes Y because the genes are in state S. We have a great many good guesses but alas no certainty. What we do have is some reasonable approach to the inductive case. Yet even here we are lacking certainty. The lacking of certainty leads to questionable assertions regarding capacity or potentiality.

We can now extend this discussion of classical concepts to our understanding of what a cancer is. As Al-Saleem has noted:

The diagnosis of "cancer" is a very traumatic and is usually associated with huge psychological, social and economic burdens to most patients and their families. It is obvious that a "modern" definition of "cancer" may not improve research and management of this rather complex disease only, but will also reduce the burden of cancer diagnosis and improve the patient-provider communications and clarify the diagnostic and therapeutic decisions. So, what is the present definition of "cancer"? This seems to be an absurd question from a person who has spent more than half a century diagnosing and researching cancer, like myself.

Indeed, it is not. Definitions should reflect what we know and the definition should not necessarily remain fixed in time if knowledge is continuously being added. For example, in the field of systematics, as we have obtained more detailed information based upon the genetics of those things we are classifying we find the trees which have been used for centuries do change and sometime dramatically. Thus, it should be the case with cancer that we should modify its classification as we progress in knowledge and understanding.

The author continues:

The National Cancer Institute (NCI) defines cancer as follows "cancerous tumors are malignant, which means they can spread into, or invade, nearby tissues. In addition, as these tumors grow, some cancer cells can break off and travel to distant places in the body through the blood or the lymph system and form new tumors far from the original tumor".

Similarly, The World Health Organization (WHO) states: "a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis". Do all lesions we call "cancer" satisfy these definitions of invasion and metastasis?

The last sentence is the most compelling. Perhaps we have been a bit too aggressive in our assertion of what is malignant and a cancer. For example, take a thyroid lesion which

histologically is identified as a FVPTC, a malignant cancer. Yet it may be circumscribed and without any vasculature. But more importantly it has no fusions or genetic changes. From the genetic perspective it is perfectly normal, namely looks genetically like every other normal cell. So, do we allow genetics to trump histology? That will be the challenge we will face now.

2 SOME DEFINITIONS

We now focus on some definitions. The definitions are critical because as we learn more about small lesions with limited to no change of metastasis, we may have to re-examine the overall nature of cancers. Moreover, we may have the opportunity to better understand the relationship between morphological changes and the genetic underpinnings.

Cancer has been with humans most likely since the beginning. As Papavramidou et al have noted some of the early understandings including that of Galen as below:

Cancer appears in medical history as early as 1600 BC in the Edwin Smith papyrus, where the oldest description of the illness exists. However, the origin of the word ‘‘cancer’’ is credited to the Hippocratic physicians, who used the terms karkinos and karkinoma in order to describe tumors. Karkinos was used for any nonhealing swelling or ulcerous formation, even hemorrhoids, whereas karkinoma was reserved for nonhealing ‘‘cancer.’’

The physicians of antiquity generally used remedies and plasters for local treatment of tumors, as well as cauterization, which was used even by the Hippocratic physicians for treatment of cancer of the pharynx. Nonetheless, in this Editorial, an attempt is made to describe ancient surgical methods that include excision of the tumor and to correlate them with modern medical practice, providing possible explanations for the surgical choices made by ancient authors. Such references were traced in the texts of the Hippocratic physicians, of Archigenes of Apamea, of Galen, of Leonides of Alexandria, and of Paulus Aegineta, ranging from the 5th century BC to the 7th century AD.

They continue with a discussion of the approach of Galen:

Almost contemporary to Archigenes, but strongly criticizing him at any given opportunity, Galen, who made a detailed categorization of abnormal growths (he even wrote a treatise named On tumors against nature), believed that cancer may appear in any part of the body, but he had seen it more often occurring in the breasts of women whose menstruation was either abnormal or inexistent. He believed that the cause of this disease is the accumulation of ‘‘residues of black bile formed in the liver during hematosis and left aside by the cleaning process taking place in the spleen.’’

These residues are created when the liver is weak, when the diet is of the nature that produces a large amount of thick blood and the spleen is weakly attracting the humor. Such a procedure produces a very thick and mud-like blood that accumulates in the veins. This is how Galen explains the appearance of black veins around the cancerous part that looks like a crab: ‘‘as the crab has legs spreading around its body, in the same way are the veins in this illness; they are spread by the abnormal tumor in a shape of crab.’’

This comparison of the cancerous tumor to a crab is actually the reason for the name of the disease, since karkinos (cancer) means crab in Greek. Additionally, Galen notes that, when such tumors ulcerate, they discharge a dark-reddish and foul-smelling secretion, suggesting that the

cause of the illness is black bile. As for treatment of cancer, Galen suggests that it is only curable at its commencement, otherwise surgery should take place.

A round incision should be made around the tumor, so that the entirety of the growth is excised. He advises the surgeon to be extremely careful because there is great danger that hemorrhage will occur and the attempt to restrain it with ligatures may affect neighboring parts with cancer. He also mentions the use of cauterization for burning of the roots of the tumor, which is a process that may also prove to be dangerous. Finally, he suggests that the physician should try to ‘‘thin’’ the blood first, with the aid of purgative medicaments and then proceed to the operation.

For centuries we have been battling this disease. Admittedly shorter life span mitigated against many cancers, especially those of older age. Now from the NCI we have the following more current definition for malignancy[3]:

A term for diseases in which abnormal cells divide without control and can invade nearby tissues.

Note first that the cells must be abnormal. Just because a cell is abnormal may or may not make is a malignant cell. The second element is dividing without control. Many "in situ" lesions divide up to a point. However, we may not really know their lifetime states. Perhaps, as if found in HGPIN, they may regress. Invasion is the third criteria. Thus, are the abnormal cells of a larger number than usual are not invading but are circumscribed, what does that mean?

Malignant cells can also spread to other parts of the body through the blood and lymph systems.

Here we have the Aristotelean concept of capability or potential. The cell may spread, but we do not know that unless they really have spread.

There are several main types of malignancy. Carcinoma is a malignancy that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a malignancy that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a malignancy that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are malignancies that begin in the cells of the immune system. Central nervous system cancers are malignancies that begin in the tissues of the brain and spinal cord. Also called cancer.

Now we consider the definition of cancer from NCI[4]:

Cancer cells differ from normal cells in many ways that allow them to grow out of control and become invasive. One important difference is that cancer cells are less specialized than normal

[3] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/malignancy

[4] https://www.cancer.gov/about-cancer/understanding/what-is-cancer

cells. That is, whereas normal cells mature into very distinct cell types with specific functions, cancer cells do not.

This is a difficult one. For example, thyroid malignancy results in thyroid like cells that go off under metastasis to other organs. Yet they still have thyroid like functions producing thyroglobulin. This is a hormone produced in search of a colloid to generate T3 and T4. Melanocytes retain much of their functions producing melanosomes and thus a met to the brain can be so identified. Thus, this claim is not dispositive.

This is one reason that, unlike normal cells, cancer cells continue to divide without stopping. In addition, cancer cells are able to ignore signals that normally tell cells to stop dividing or that begin a process known as programmed cell death, or apoptosis, which the body uses to get rid of unneeded cells.

Cancer cells may be able to influence the normal cells, molecules, and blood vessels that surround and feed a tumor—an area known as the microenvironment. For instance, cancer cells can induce nearby normal cells to form blood vessels that supply tumors with oxygen and nutrients, which they need to grow. These blood vessels also remove waste products from tumors.

How can this assertion be shown in a localized lesion? Again, we can consider HGPIN or NIFTP. Oftentimes what we observe is a slight proliferation and possible cellular abnormalities. Are the cell abnormalities induced endogenously or exogenously? That is a challenge in a localized lesion. Adenomas are also classic examples. They are a proliferation of cells with some possible cellular abnormalities. For example, we may see mitotic events, enlargement of a nucleus, enlargement of the nucleolus. Are these alone dispositive for a cancer?

Cancer cells are also often able to evade the immune system, a network of organs, tissues, and specialized cells that protects the body from infections and other conditions. Although the immune system normally removes damaged or abnormal cells from the body, some cancer cells are able to "hide" from the immune system. Tumors can also use the immune system to stay alive and grow. For example, with the help of certain immune system cells that normally prevent a runaway immune response, cancer cells can actually keep the immune system from killing cancer cells.

The immune response effects are of interest. Much of current immunotherapy is based upon the recognition that cancer cells can protect themselves despite the fact that they can be determined to be attacked by the immune system[5].

As Hanahan and Weinberg have noted:

Arguably the most fundamental trait of cancer cells involves their ability to sustain chronic proliferation. Normal tissues carefully control the production and release of growth-promoting signals that instruct entry into and progression through the cell growth and division cycle,

[5] https://www.researchgate.net/publication/314090163_Cancer_Immunotherapy_A_Systems_Approach

thereby ensuring a homeostasis of cell number and thus maintenance of normal tissue architecture and function.

Cancer cells, by deregulating these signals, become masters of their own destinies. The enabling signals are conveyed in large part by growth factors that bind cell-surface receptors, typically containing intracellular tyrosine kinase domains. The latter proceed to emit signals via branched intracellular signaling pathways that regulate progression through the cell cycle as well as cell growth (that is, increases in cell size); often these signals influence yet other cell-biological properties, such as cell survival and energy metabolism.

Nice, but how do we apply this principle? Must we wait until the cells proliferate, chronically? There are many cancers in what is considered the in-situ state where at best one has some morphological identification. Are these delimited non proliferated calls which exhibit morphological changes really cancers?

Cancer for the most part is a genetic disorder. Homeostasis of normal cells means that there is a place for everything and everything in its place. When cells no longer follow the "rules" then we consider this to be a cancer, most of the time. For example, a wart is often the hyperplasia that results from some viral infection. But the hyperplasia is localized. A breast cancer is a lesion where the cells are growing as a result of some failed genetic mechanism. However, in a myelodysplastic syndrome, MDS, the cells proliferate aberrantly due to an epigenetic defect, methylation. Is MDS also a genetic defect as BRCA is in the breast cancers?

The reasons why we ask these questions is driven by the explosions of some "cancers" which are really carcinoma in situ and may never metastasize. Thus, as asked by Al-Saleem have our abilities to identify more and more led us to an over exuberance? Or perhaps as I have suggested, the histological diagnosis must be aligned with the genomic assessment for an integrated diagnosis[6].

It is also worthwhile to examine some of the perspectives on cancer in an historical context. In the 1938 book on Cancer by Cutler and Buschke we see that at that time there was a categorization with diagnosis occurring only after the lesions were clearly noticeable. The approach was treatment after the fact. For example, their discussion on prostate cancer had suggested rectal exams as a new technique and surgery or radiation as the treatment. The discussion on biopsies was paltry to say the least. In fact they suggested that for the most part biopsies were unnecessary since the disease was at the time of recognition obviously self-evident.

[6] https://www.researchgate.net/publication/334429457_miRNAs_Genes_and_Cancer_Cytology

3 SOME STATISTICS

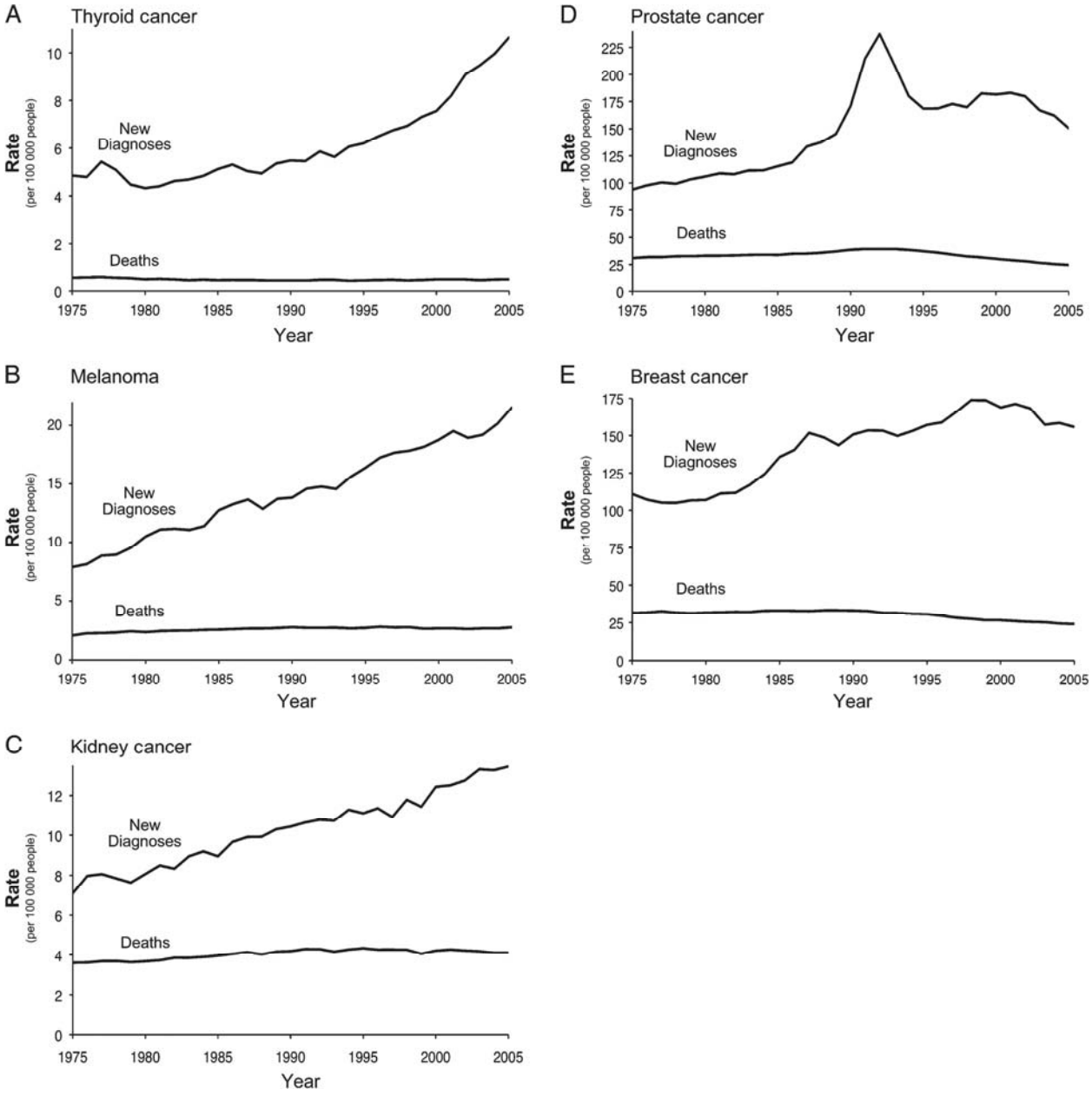
There has been a trend in many cancers of increasing incidence but stead mortality. Incidence is changing because of improved surveillance and mortality remaining constant or even decreasing due to improved treatment. But that does not appear to tell the whole story. As Welch and Black have noted:

…the phenomenon of cancer overdiagnosis—the diagnosis of a "cancer" that would otherwise not go on to cause symptoms or death. We describe the two prerequisites for cancer overdiagnosis to occur: the existence of a silent disease reservoir and activities leading to its detection (particularly cancer screening).

We estimated the magnitude of overdiagnosis from randomized trials: about 25% of mammographically detected breast cancers, 50% of chest x-ray and/or sputum-detected lung cancers, and 60% of prostate-specific antigen–detected prostate cancers. We also review data from observational studies and population-based cancer statistics suggesting overdiagnosis in computed tomography–detected lung cancer, neuroblastoma, thyroid cancer, melanoma, and kidney cancer. To address the problem, patients must be adequately informed of the nature and the magnitude of the trade-off involved with early cancer detection.

Equally important, researchers need to work to develop better estimates of the magnitude of overdiagnosis and develop clinical strategies to help minimize it.

We now consider some of the recent observations regarding a collection of cancers in their early stages which may or may not ever become a true malignancy, namely an entity which has metastasized. The figures below are from Welch and Black and tell an interesting tale, albeit a bit problematic.

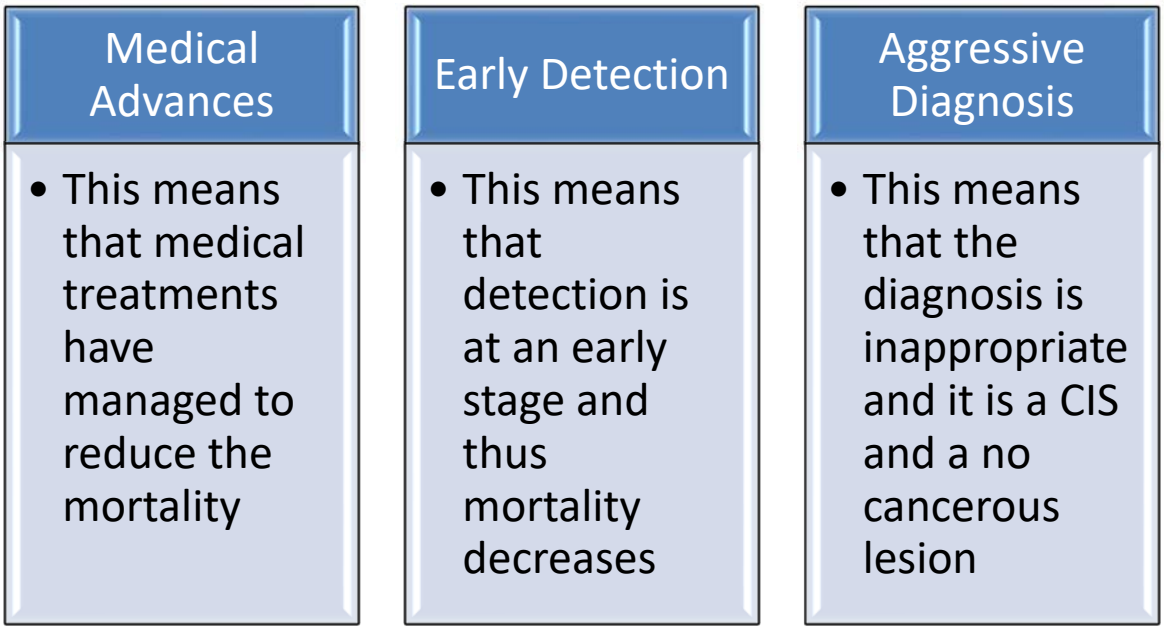


The Figures above show the following:

1. New diagnoses are increasing over time

2. Mortality is remaining constant

3. The reasons for this may be at least twofold. First, medicine has advanced to mitigate against mortality, a reasonable conclusion. Second, earlier stage cancer are being caught and resulting in lower mortality. Third, "cancers" are being identified which would never have resulted in mortality.



Welch and Black conclude:

Overdiagnosis—along with the subsequent unneeded treatment with its attendant risks—is arguably the most important harm associated with early cancer detection. The impact of false-positive test results is largely transitory, but the impact of overdiagnosis can be life-long and affects patients' sense of well-being, their ability to get health insurance, their physical health, and even their life expectancy.

For clinicians and patients, overdiagnosis adds complexity to informed decision making: Whereas early detection may well help some, it undoubtedly hurts others. In general, there is no right answer for the resulting trade-off—between the potential to avert a cancer death and the risk of overdiagnosis. Instead, the particular situation and personal choice have to be considered. Often, the decision about whether or not to pursue early cancer detection involves a delicate balance between benefits and harms—different individuals, even in the same situation, might reasonably make different choices.

To address overdiagnosis, it is important to ensure that patients are adequately informed of the nature and the magnitude of the trade-off involved with early detection. This kind of discussion has been widely advocated as part of PSA screening but is nevertheless challenging for patients. They must first clearly understand the nature of the trade-off that although early diagnosis may offer the opportunity to reduce the risk of cancer death, it also can lead one to be diagnosed and treated for a "cancer" that is not destined to cause problems. Then, they must understand the magnitude of the trade-off. Each idea will be foreign and difficult, so they must be presented very

clearly. We believe that this is best done through the construction of simple one-page balance sheets that frame the trade-off. We have provided one such example for screening mammography

4 CARCINOMA IN SITU (CIS) ET AL

We now will examine several of the CIS that are prevalent.

As Al-Saleem notes the current confusion regarding the definition of CIS:

Atypical epithelial proliferations called "carcinoma in-situ" may not qualify for the name "cancer"; the lowest-grade ductal carcinoma in situ lesions behave more like atypia, with risks for invasive cancer at 10 years in patients with low-grade lesions similar to risks in patients diagnosed with atypia. The so-called lobular carcinoma in situ is generally considered a marker of higher risk of developing mammary carcinoma rather than a non-invasive malignancy itself. The low grade non-invasive papillary urothelial "carcinoma" rarely if ever invades the lamina propria and may never metastasize; still we call it "cancer".

In certain organs, e.g. gastrointestinal tract, the term carcinoma-in situ was abandoned in favor of "high grade dysplasia" without obvious effect on the rigorous management and/or follow up as needed. HPV associated squamous lesion that used to be called carcinoma in-situ of the cervix is now named "grade III cervical intraepithelial neoplasia. Yet, a morphologically and etiologically similar lesion in the oral cavity or oropharynx is still called "carcinoma in situ"!

Thus, we ask, just what is CIS? Is it a misnomer and why do we call it CIS in some cases and not in others? One may even ask if this is done for legalistic or billing purposes, albeit placing many patients in considerable discomfort not truly understanding their condition. We consider four cases and try to obtain some insight as to this issue.

4.1 PCA IN SITU

Prostate cancer, PCa, is a very common malignancy amongst men, and often approaches 100% in men in their 90s. It has generally two forms, albeit based on some clinical evidence only. One form, the dominant, is very slow growing and generally indolent. This form may represent up to 95% of all PCa. The second form is highly aggressive and with very high mortality and is represented by about 5% of the cases[7].

HGPIN is represented by morphological changes in prostate cells in the acinar or glandular locations. It generally is a complex set of growth patterns of new cells whose morphological appearance is similar to but not identical to the existing cells in the gland. The new cells clearly have form and shape that demonstrates pre-malignant morphology, with enlarge and prominent nucleoli.

From the paper by Putzi and DeMarzo we have:

T*he high-grade form of prostatic intraepithelial neoplasia (PIN) has been postulated to be the precursor to peripheral zone carcinoma of the prostate. This is based on zonal co-localization,*

[7] https://www.researchgate.net/publication/264960277_Prostate_Cancer_A_Systems_Approach

morphologic transitions, and phenotypic and molecular genetic similarities between high-grade PIN and carcinoma. Although high-grade PIN is thought to arise from low-grade PIN, which in turn is thought to arise in normal or "active" epithelium, little is known whether truly normal epithelium gives rise to PIN or whether some other lesion may be involved.

Focal atrophy of the prostate, which includes both simple atrophy and postatrophic hyperplasia, is often associated with chronic, and less frequently, acute inflammation. Unlike the type of prostatic atrophy associated with androgen withdrawal/ blockade (hormonal atrophy), epithelial cells in simple atrophy/postatrophic hyperplasia have a low frequency of apoptosis and are highly proliferative. In addition, hormonal atrophy occurs diffusely throughout the gland and is not usually associated with inflammation.

To simplify terminology and to account for the frequent association with inflammation and a high proliferative index in focal atrophy of the prostate, we introduced the term "proliferative inflammatory atrophy" (PIA).

In a similar manner in a review paper by O'Shaughnessy et al on multiple intraepithelial neoplasia the authors state the following regarding HGPIN:

The evidence that PIN is a morphological and genetic precursor to prostate cancer is extensive and conclusive ...

When examined microscopically, PIN lesions are characterized by collections of proliferative prostatic epithelial cells confined within prostatic ducts that exhibit many morphological features of prostate cancer cells, including architectural disorganization, enlarged cell nuclei and nucleoli. …

In addition to the similarity of the cellular morphologies of HGPIN and invasive lesions, evidence that HGPIN is a precursor of prostatic adenocarcinoma includes the multifocality of both lesions and the presence of carcinoma in foci of PIN; among older men, foci of PIN are found in 82% of prostates with carcinoma but in only 43% of normal prostates.

PIN is frequently located in the peripheral zone of the prostate, the site at which 70% of prostatic carcinomas occur. Additional similarities include enhanced proliferative activity of both PIN and carcinoma (3-fold that of benign tissue), cytokeratin immunoreactivity, lectin binding, and loss of blood group antigen with both PIN and carcinoma.

Prevalence of PIN and its temporal association with invasive cancer are illustrated by the known 40–50% PIN incidence in men 40–60 years of age, evolving into the 40–50% incidence of prostate cancer in men 80 years of age. Autopsy data reveal that PIN lesions appear in the prostates of men in their 20s and 30s in the United States, preceding the appearance of prostate cancer lesions by as many as 10 years …

African-American men, who are at higher risk of prostate cancer mortality, appear to have a greater extent of PIN at any given age. PIN and prostate cancer lesions share a number of somatic genome abnormalities, including loss of DNA sequences at 8p and increased GSTP1 CpG island DNA methylation, among others.

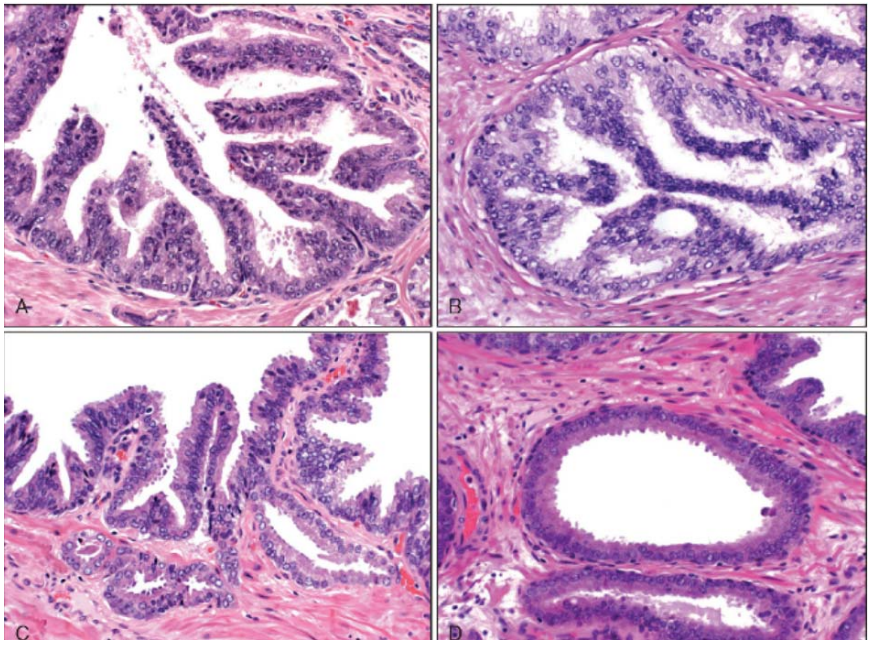
Finally, transgenic mouse strains prone to developing prostate cancers typically develop PIN lesions in advance of the appearance of invasive cancer. PIN lesions are always asymptomatic and cannot currently be diagnosed or detected by any reliable means other than examination of prostate tissue histologically. In autopsy studies, the incidence and extent of PIN increases with age, as does the incidence of prostate cancer.

Notwithstanding the correlation, there does not seem to be causality. In addition, the authors do indicate that HGPIN can be reduced but they seem to fail to speak to the issue of total remission without any treatment. The question is therefore, is PIN a precursor of PCa? If it is or is not, is PIN the result of a genetic change as has been postulated by many? It would seem clear that the existence of remission of PIN would imply that it is not at all necessarily a precursor and furthermore that it is not necessarily a genetic change for all PIN. That is can there be a morphological PIN that is genetic and not remissionable and one which is remissionable. Remissionable implies the existence of apoptosis, that is a natural cell death or perhaps a cell death due to some immune response.

Noe let us consider Welch and Black who note:

Let us consider the data of two investigators who made age- specific estimates of the reservoir of prostate cancer from autopsies… examined the prostate glands of 525 American men who died in an accident; … examined 212 Greek men who died of other causes and were not found to have palpable prostate cancer. Because additional estimates based on specimens obtained by radical cystectomy are similarly variable, it is clear that the reservoir of potentially detectable prostate cancer is highly age dependent and

The following are from Yang and depict High Grade PIN, also a CIS of the prostate.



Different patterns of high-grade prostatic intraepithelial neoplasia (HGPIN). A, Micropapillary pattern. B, Cribriform pattern. C, Tufting. D, Flat.

The above comments demonstrate several factors. First the prostate cells are still in a glandular fashion and the fundamental structure remains. Second, the prostate composed of basal and luminal cells has a proliferation of the luminal cells. Third, the papillary forms show some papilla of curved growth as compared to the more uniform structure. Fourth, HGPIN generally is diagnosed via the cell proliferation and does not include detailed single cell forms.

4.2 MELANOMA IN SITU

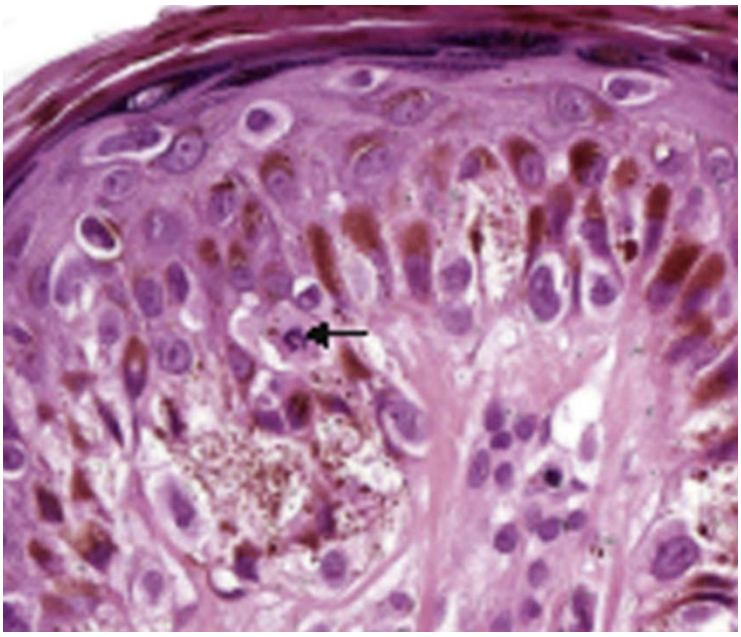
Melanoma is a highly aggressive cancer of the skin and it metastasizes rapidly. Recently many types of immunotherapy can abate the cancer and place it into remission. However it can often be so aggressive that one is as of yet unable to mitigate it in any manner[8].

Welch and Black note:

For melanoma, the rate of diagnosis has almost tripled (from 7.9 per 100 000 to 21.5 per 100 000). Again, the rate of death is generally stable (little change in the past 15 years). Although there may be an element of a true increase in clinically significant melanoma, these data suggest that most of the increase in diagnosis reflects overdiagnosis. The issue of overdiagnosis is well known to dermatologists. Because almost all the new diagnoses are localized (or in situ) melanomas and because their appearance almost perfectly tracks the increase in population skin biopsy rates, overdiagnosis is likely the predominant explanation for the rise.

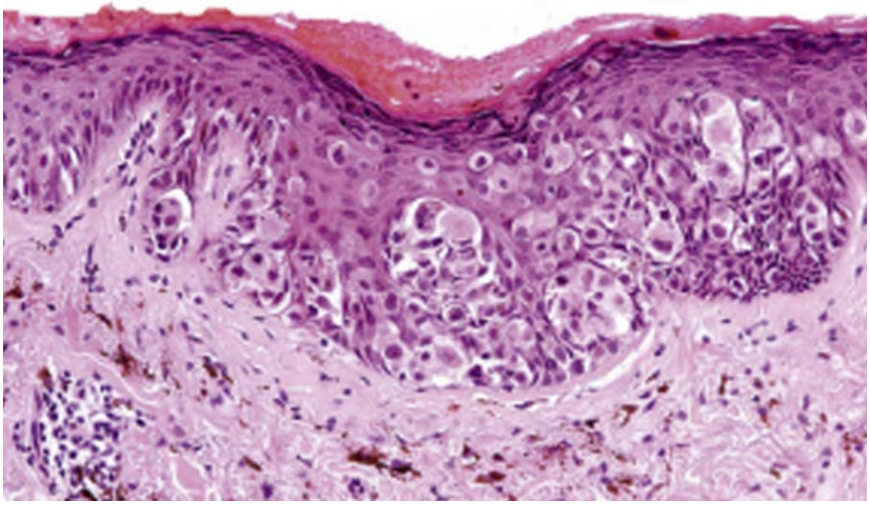
We include a sample shown below. Here we look at single cells, the melanocytes, and we see changes in the cell itself/

[8] https://www.researchgate.net/publication/264960157_Melanoma_Genomics



In-situ melanoma: a mitotic figure is present in the mid left field (arrowed)[9].

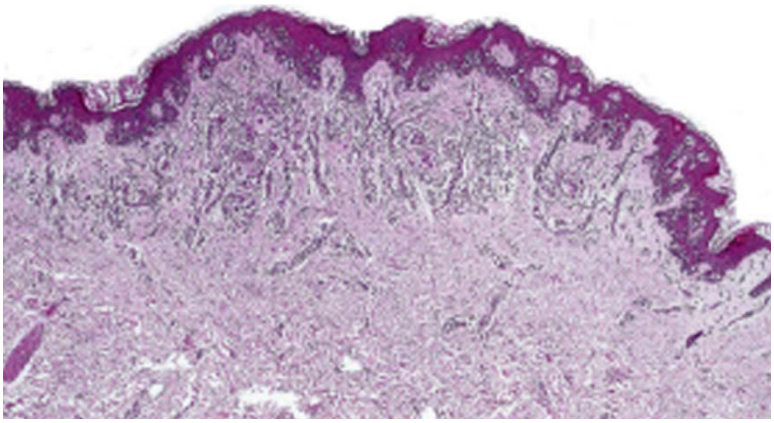
Then we look at cells in a more grouped manner as shown below. Normally the melanocytes reman at the basal layer of the epidermis. However, they can start moving upward and this is indicated in the figure below. The lack of stable location can be genetically related to loss of E cadherin.



In-situ melanoma: this example shows scattered tumor cells, both singly and as nests, at all levels of the epidermis (pagetoid spread).

The figure below is a full-blown melanoma. Note that the movement is now down to the dermis as noted below.

[9] Mitotic figure depict the chromosome separating in mitosis.



Melanoma: low-power view showing conspicuous junctional activity. Nests of tumor cells are present in the papillary dermis and there is a heavy lymphohistiocytic infiltrate.

4.3 DCIS

Breast cancer (BCa) is the alter ego of prostate cancer. It occurs in women at a younger age than PCa in men but has many elements in common.

From Hanna et al:

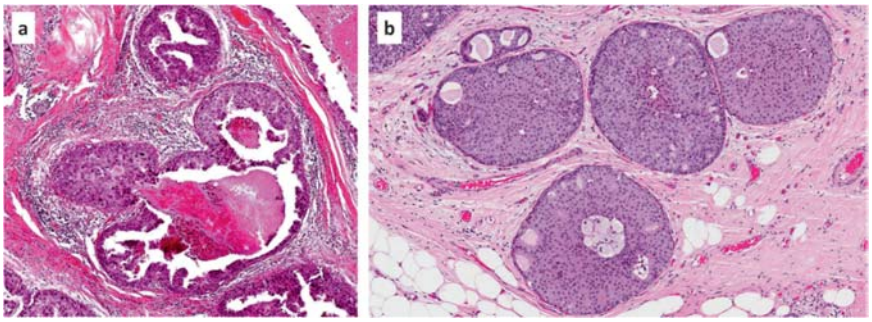
Ductal carcinoma in situ (DCIS) is a neoplastic proliferation of mammary ductal epithelial cells confined to the ductal-lobular system, and a non-obligate precursor of invasive disease. While there has been a significant increase in the diagnosis of DCIS in recent years due to uptake of mammography screening, there has been little change in the rate of invasive recurrence, indicating that a large proportion of patients diagnosed with DCIS will never develop invasive disease.

The main issue for clinicians is how to reliably predict the prognosis of DCIS in order to individualize patient treatment, especially as treatment ranges from surveillance only, breast-conserving surgery only, to breast-conserving surgery plus radiotherapy and/or hormonal therapy, and mastectomy with or without radiotherapy. We conducted a semi-structured literature review to address the above issues relating to "pure" DCIS.

Here we discuss the pathology of DCIS, risk factors for recurrence, biomarkers and molecular signatures, and disease management. Potential mechanisms of progression from DCIS to invasive cancer and problems faced by clinicians and pathologists in diagnosing and treating this disease are also discussed. Despite the tremendous research efforts to identify accurate risk stratification predictors of invasive recurrence and response to radiotherapy and endocrine therapy, to date there is no simple, well-validated marker or group of variables for risk estimation, particularly in the setting of adjuvant treatment after breast-conserving surgery.

Thus, the standard of care to date remains breast-conserving surgery plus radiotherapy, with or without hormonal therapy. Emerging tools, such as pathologic or biologic markers, may soon change such practice.

We show some examples below from Hanna et al.



Hematoxylin- and eosin-stained sections of DCIS. a High-grade DCIS with comedonecrosis and abundant stromal tumor-infiltrating lymphocytes. b Low-grade DCIS without necrosis. DCIS, ductal carcinoma in situ

As shown, the CIS consisted of localized proliferation along with putative changes in the cells. To best understand the cellular changes one must examine the cells independently.

As Berg notes in an Editorial on this topic:

The diagnosis and management of ductal carcinoma in situ (DCIS) is controversial. With widespread mammography screening, diagnosis of DCIS became more prevalent. Some are uncertain whether this has translated into a decrease in invasive cancer and a subsequent decline in breast cancer mortality. Part of the concern has been that frequently the treatments of DCIS are as extensive as for invasive cancer with a similar panoply of risks. A straightforward approach to selecting the optimum therapy— defined here as the minimum needed to avoid recurrence, particularly with an invasive component—is needed.

Many solutions have been proposed, but none has gained wide acceptance. For example, the Van Nuys Prognostic Index has been in common use for decades. Several randomized clinical trials have compared lumpectomy alone to lumpectomy followed by radiation treatment, but no subset analysis of these results has found a group that does not benefit from radiation with a lower in-breast recurrence risk.

We can examine some of the related genomic issues of DCIS. As Russnes et al have noted:

Complex rearrangements as defined by CAAI occurred in all subgroups, and CAAI had a strong prognostic impact independent of other factors, even if it only occurred on one chromosomal arm. The mechanisms behind complex rearrangements are not completely understood, but one type can be explained by breakage-fusion-bridge cycles because of double-strand repair defects resulting in high-level amplicons with intermittent deletions. ***Because high-level amplicons are***

seen even in DCIS and in diploid tumors, this opens the possibility for a distinct subtype of carcinomas having complex alterations at an early stage of progression ("de novo complexity").

Lari and Kuerer note:

Understanding of the biology and clinical behavior of ductal carcinoma in situ (DCIS) is currently inadequate. The aim of this comprehensive review was to identify important molecular biological markers associated with DCIS and candidate markers associated with in-creased risk of ipsilateral recurrence after diagnosis of DCIS.

A comprehensive systematic review was performed to identify studies published in the past 10 years that investigated biological markers in DCIS. To be included in this review, studies that investigated the rate of biological expression of markers had to report on at least 30 patients; studies that analyzed the recurrence risk associated with biomarker expression had to report on at least 50 patients.

There were 6,252 patients altogether in our review. Biological markers evaluated included steroid receptors, proliferation markers, cell cycle regulation and apoptotic markers, angiogenesis-related proteins, epidermal growth factor receptor family receptors, extracellular matrix-related proteins, and COX-2. Although the studies in this review provide valuable preliminary information regarding the expression and prognostic significance of biomarkers in DCIS, common limitations of published studies (case-series, cohort, and case-control studies) were that they were limited to small patient cohorts in which the extent of surgery and use of radiotherapy or endocrine therapy varied from patient to patient, and variable methods of determining biomarker expression. These constraints made it difficult to interpret the ab-solute effect of expression of various biomarkers on risk of local recurrence.

No prospective validation studies were identified. As the study of biomarkers are in their relative infancy in DCIS compared with invasive breast cancer, key significant prognostic and predictive markers associated with invasive breast cancer have not been adequately studied in DCIS. There is a critical need for prospective analyses of novel and other known breast cancer molecular markers in large cohorts of patient with DCIS to differentiate indolent from aggressive DCIS and better tailor the need and extent of current therapies.

The authors of the above have provided an extensive review of a multiple set of putative genetic markers but their conclusion is limited as noted in the following:

It was difficult to elucidate the prognostic importance of the biomarkers investigated in this comprehensive review because of heterogeneous treatment approaches and often conflicting results. Although the studies in this review provide valuable information on the diagnostic and prognostic significance of the studied markers, another factor that limits our ability to draw conclusions on the basis of the information in this review is the fact that many of the studies reviewed included only small numbers of patients. Other studies included groups of patients treated with different therapies, and in some studies the treatment was inconsistent. In addition, several studies included patients who had received endocrine therapy or radiotherapy, while other studies did not. This heterogeneous treatment makes it hard to assess clinical outcome. In

conclusion, novel and key breast cancer biological markers need to be studied prospectively in large cohorts of patient to differentiate indolent from aggressive DCIS and tailor the need and extent of therapies.

The authors provide the following Table as putative targets.

Category	*Examples*
Steroid receptors	Estrogen receptor, progesterone receptor, and androgen receptor
Proliferation marker	Ki-67
Cell cycle regulation and apoptotic markers	cyclin D1, cyclin A, cyclin E, p16, p21, p27, p53, Bcl-2, Bax, Survivin, c-myc, and retinoblastoma
Angiogenesis related proteins	Vascular endothelial growth factor and heparanase-1
Epidermal growth factor receptor family	HER1, HER2, HER3, and HER4
Extracellular matrix related proteins	CD10 Secreted protein acidic and rich in cysteine
Other biological marker(s)	COX-2

However, there is no definitive set to be examined. A similar paper by Vincent-Salomon et al discusses the same issue as follows:

In conclusion, our data show that DCIS already displays the molecular diversity observed in IDC and, therefore, can be classified according to molecular criteria distinguishing ERBB2-amplified DCIS, usually high-grade, ER negative with frequent TP53 mutations, from luminal DCIS corresponding to low/ intermediate-grade, ER positive with a very low rate of TP53 mutations.

In our series, only three cases were classified as triple negative and only one was classified as basal-like DCIS, which confirms that this last entity is rare among DCIS. Further studies are needed to define whether a classification of DCIS based on molecular markers may help to more accurately define cases associated with a higher risk of recurrence. And finally, genomic/transcriptomic correlations represent a promising tool to identify new genes and pathways important in early breast carcinogenesis.

The search goes on with DCIS.

4.4 NFTP

Thyroid cancer is substantially less than prostate or breast and comes in a variety of forms. It generally has a higher incidence in females and at a younger age. In older adults it is less frequent and may be of limited aggressiveness if contained. On the other hand, it can be highly

aggressive and lethal if undetected before it becomes anaplastic. The anaplastic variety, albeit quite rare, is lethal in months[10].

Welch and Black note:

Harach et al. systematically examined the thyroid gland in 101 autopsies. They examined slices of thyroid tissue taken every 2.5 mm and found at least one papillary carcinoma in 36% of Finnish adults. Because many of the cancers were smaller than the width of the slices, they reasoned that they were missing some. Given the number of small cancers they did find and the number that they estimated they had missed (which was a function of size), ***Harach et al. concluded that the prevalence of histologically verifiable papillary carcinoma would be close to, if not equal to, 100% if one could look at thin enough slices of the gland.***

Another variant is the NIFTP. Shrestha et al have characterized it as:

The re-naming of noninvasive follicular variant papillary thyroid cancer to the apparently non-malignant, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) impacts the prevalence of malignancy rates, thereby affecting mutation frequency in papillary thyroid cancer. Preoperative assessment of such nodules could affect management in the future. The original publications following the designation of the new nomenclature have been extensively reviewed.

With the adoption of NIFTP terminology, a reduction in the follicular variant of papillary thyroid cancer (FVPTC) prevalence is anticipated, as is a modest reduction of papillary thyroid cancer (PTC) prevalence that would be distributed mainly across indeterminate thyroid nodules.

Identifying NIFTP preoperatively remains challenging. RAS mutations are predominant but the presence of BRAF V600E mutation has been observed and could indicate inclusion of the classical PTC. The histological diagnosis of NIFTP to designate low-risk encapsulated follicular variant papillary thyroid cancers (EFVPTCs) would impact malignancy rates, thereby altering the mutation prevalence. The histopathologic criteria have recently been refined with an exclusion of well-formed papillae. The preoperative identification of NIFTP using cytomorphology and gene testing remains challenging.

They go on to characterize it specifically as:

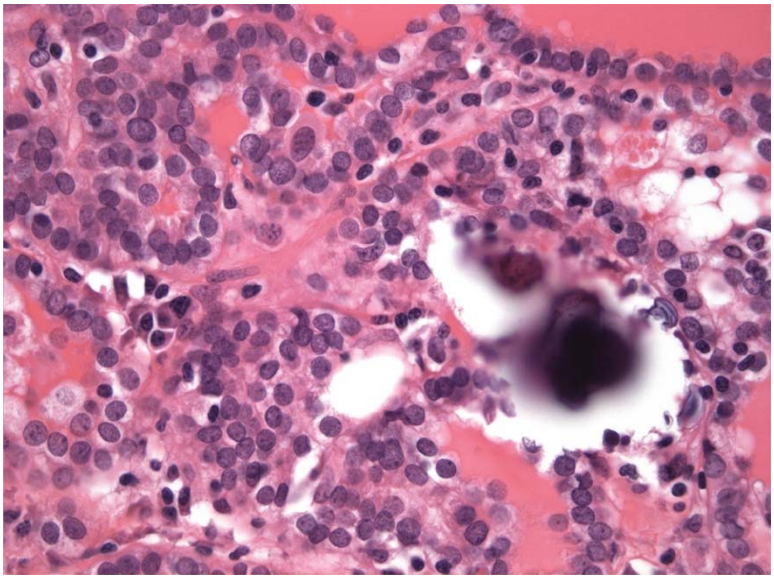
1. *Encapsulation or clear demarcation*
2. *Nuclear score 2–3*[11]
3. *No vascular or capsular invasion*
4. *No tumor necrosis*
5. *No high mitotic activity (<3/HPF) Follicular growth pattern with:*

[10] https://www.researchgate.net/publication/331935614_Thyroid_Cancer_Seek_and_Ye_Shall_Find

[11] We shall be discussing this metric shortly.

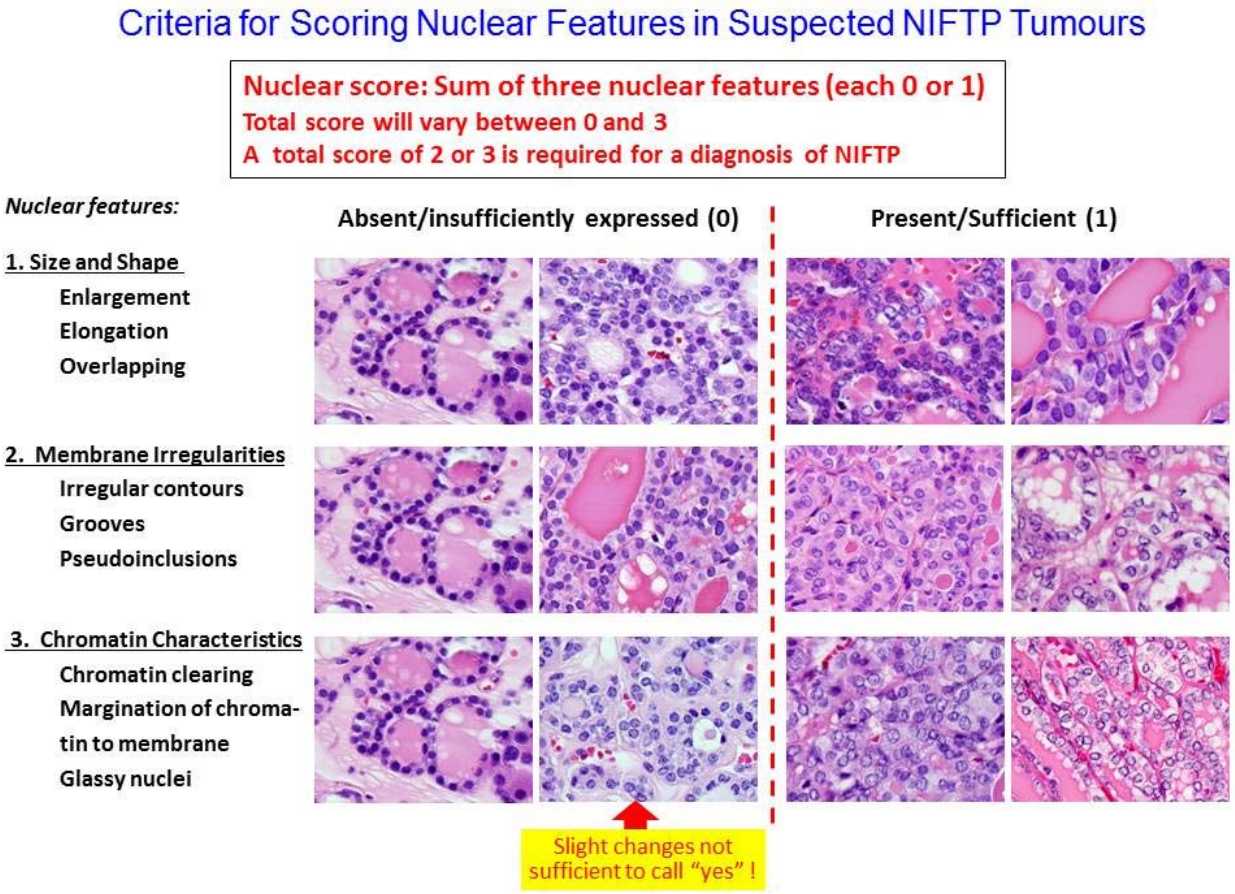
6. *<1% Papillae (criteria modified in 2018 to "no well-formed papillae") No psammoma bodies <30% solid/trabecular/insular growth pattern*

Thus, if one sees a micro FVPTC, fully encapsulated, no vascularization, and a singular lesion with no nodes, and no expression of fusion or genetic mutations, is this a carcinoma? Is morphology of the cells the telling sign, is the genetic profile more compelling, or what? We now examine some histological factors.



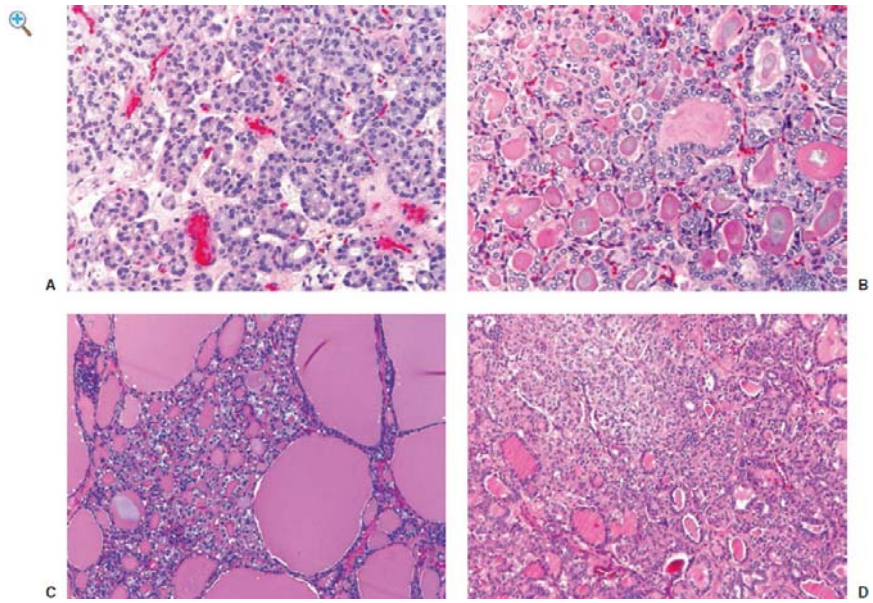
The following is a graphic depicting the analysis of the concept of nuclear score as noted previously[12].

[12] http://thyroid2018.com/images/NIFTP%20nuclei.jpg from http://www.pathologyoutlines.com/topic/thyroidglandNIFTP.html



The above is from Jug. The nuclear score is a cell by cell analysis to ascertain if the cells meet the three general specifications; (i) size and shape, (ii) membrane irregularities, (iii) chromatin characteristics. For each, if there is a sufficient number, then a measure is recorded. As we have noted previously this is a complicated and highly professional task on the part of the pathologist. It also appears to be independent of the genomic artifacts which may exist.

Another view can be obtained from Nikiforov et al as we show below examples of NIFTP:



The authors note on the Figure above the following:

*Growth patterns of **noninvasive follicular thyroid neoplasm** with **papillary-like nuclear features** (NIFTP). The tumor may be composed uniformly of very small*

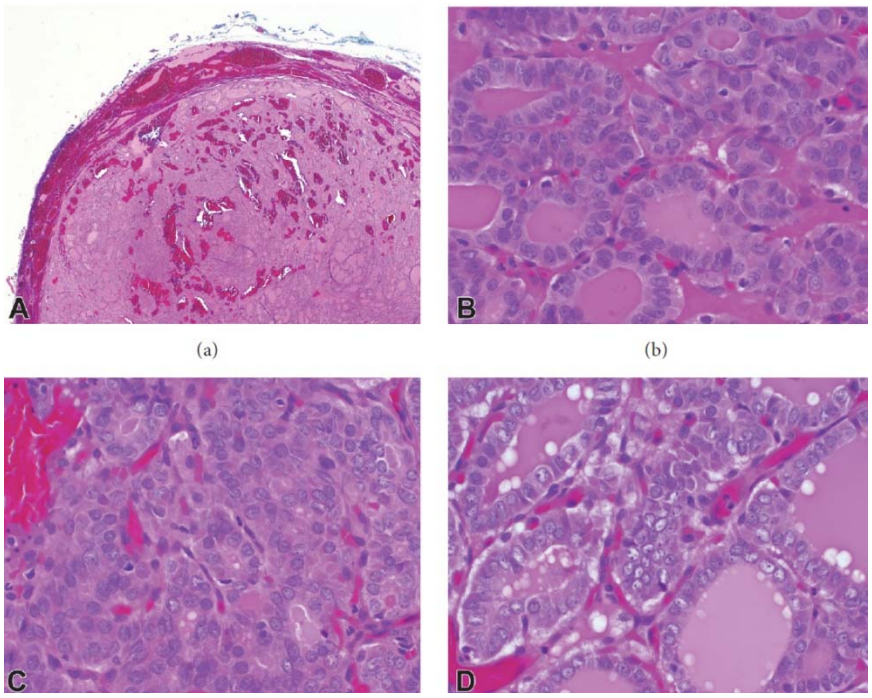
(A) or small- to normal-sized

(B) follicles or demonstrate a wide variability in the size of follicles with mostly very large follicles intermixed with focal areas composed of small follicles

(C). Small areas of solid growth are seen in this tumor

(D), which comprises <30% of the tumor volume and therefore does not trigger the exclusion criterion for NIFTP.

In a similar manner we depict the images from Jug on the NIFTP cellular presentation.



Jug et al note on the above Figures as follows:

H&E images of NIFTP: (a) low-power (2x) view demonstrating a well-circumscribed lesion with follicular architecture. No vascular or capsular invasion is present. (b, c, d) High-power (40x) images demonstrating ***nuclear enlargement, crowding, optical clearing, and grooves***[13]

We have discussed the genetic elements previously as noted. The argument here is; is there a genetic set of markers which will indicate a causative driver for proliferation and metastatic change. Should we remove all NIFTP lesions, should we remove all FVPTC lesions not fully meeting NIFTP criteria?

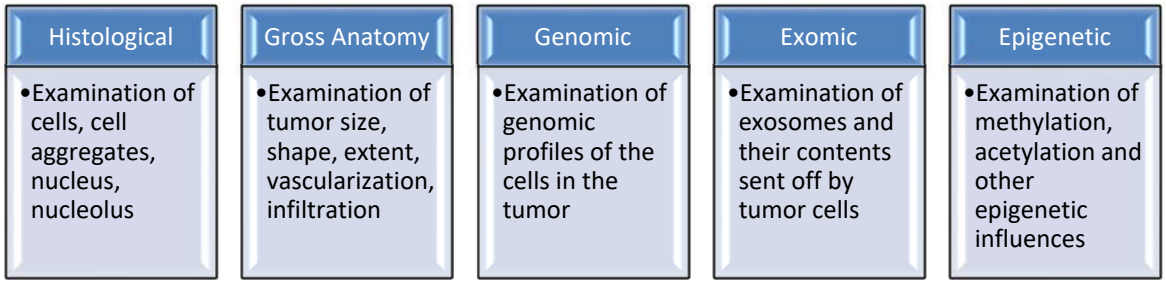
[13] From Jug et al

5 OBSERVATIONS

Clearly there must be some addressing of just what is a cancer and what is not. We present several observations and some possible suggestions. As is usual, these are at best suggestive.

5.1 WHAT IS THE NEXUS BETWEEN CELLULAR MORPHOLOGY AND GENOMIC EXPRESSIONS?

Some eighty years ago as we have noted there was little biopsy results performed. In the past two decades there has been monumental growth in understanding the genetic structure of many cancers. In between we have classic histology in examining cells and clusters of cells and determining their malignant potential. The next step must be the correlation between histology and genetic makeup. As of this time the results are somewhat orthogonal.



The above depicts many dimensions. Clearly, we have histological. We have had for ages the gross anatomic descriptions dating to Galen and before, the genomic we are in the midst of, the exomic describes the signals sent out by the cells, and the epigenetic which can represent a whole new dimension in cancer understanding.

5.2 IS "CARCINOMA IN SITU" (CIS) A VIABLE TERM?

Many histological determinations assert the lesion to be a CIS. That means the cells histologically present artifacts consistent with a mass which has metastatic potential or capacity. Yet we do not know if that is really the case.

The NCI defines CIS as follows[14]:

A group of abnormal cells that remain in the place where they first formed. They have not spread. These abnormal cells may become cancer and spread into nearby normal tissue. Also called stage 0 disease.

The above definition has the following elements:

1. *Abnormal cells*: this is a broad statement because from time to time there may appear abnormal cells which in turn may disappear. We have seen this in HGPIN where sometimes there is substantial amounts and then upon a set of re-biopsies, they disappear[15].

2. *Remain in Place…have not spread:* An adenoma of the colon can be suspicious but for the most part it remains in place. Lipomas remain in place, yet the cells are less abnormal than other alleged CIS.

3. *May become cancer*: Here the definition uses the transition to cancer in its own definition. Recall our earlier definition from NCI on what a cancer is.

4. *Spread into nearby normal tissue*: Spreading entails two elements. First movement from point A to other points. Second a proliferation of cells associated with the new locations. But one must ask if it is just limited to nearby cells? Consider melanoma in situ. The melanocytes move, and they may proliferate but all is done in the epidermal layers. Is this a non-spreading but not remaining in place lesion?

At no point in the definition do we see the term capacity or potential. We do see the term "may become". One wonders if that is a mere softening for the public or a reflection of uncertainty of potentiality.

5.3 AT WHAT POINT DOES A COLLECTION OF CELLS BECOME A CANCER, MALIGNANT?

The question is a critical one in that we can see a proliferation of cells in a prostate gland, namely a multiplication of luminal cells overlaying one another. Is that equivalent to an adenoma in the colon? Currently it is a CIS. Also, for a melanocyte, if there are a collection at the rete, a collection up among the keratinocytes? Is even a collection a dispositive measure?

5.4 WHAT ARE THE DISPOSITIVE MARKERS OF A CANCER?

[14] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/carcinoma-in-situ

[15] https://www.researchgate.net/publication/325047485_PROSTATIC_INTRAEPITHELIAL_NEOPLASIA_PROGRESSION_REGRESSION_A_MODEL_FOR_PROSTATE_CANCER

This seems to be a tug of a between histological descriptives and genomic markers. Are the histological markers such as characteristics of nuclei enough? The same for genomic markers. BRAF V600 is seen in many cells and is a known marker but not quite pathognomonic.

5.5 IF CANCERS HAVE STEM CELLS, DO CIS HAVE STEM CELLS AS WELL?

Stem cells have been acknowledged as the sources of and drivers of many cancers. We have examined these in many cancers[16], [17]. Now in assessing CIS, is it also essential to identify a stem cell as well? If so then do we need stem cells to assert a carcinoma?

5.6 IS THERE A BRIGHT LINE DISTINCTION BETWEEN CIS AND CANCER?

When does a CIS become a cancer? This seems to be a significant question. Is it inevitable? Have we "caught it just in time" type of question? Namely to be able to give an adequate answer we need to have some dividing point established.

5.7 WORDS MEAN SOMETHING

As we noted at the beginning, what we call something has effects. This is especially true for a patient. Patients are not the best listeners, if the hear a word which incites fear then perhaps all that follows gets blocked. Thus, we should be concerned about the words, and the words must reflect the facts. Medieval physicians such as Gadsden, Mondino, Gordon, and others often relied as much on grammar, logic, and rhetoric in dealing with patients. They knew that what a patient heard and how they responded was as powerful as the limited medical arts they had available to them.

[16] https://www.researchgate.net/publication/301542243_Cancer_Stem_Cells_and_Cancer_of_Origin_Redux

[17] https://www.researchgate.net/publication/301222986_Prostate_Cancer_Stem_Cells

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