BLADDER CANCER: AN INTERESTING SET OF DIAGNOSTIC OPTIONS

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White Paper No 168
October, 2019

Bladder cancer has a moderate incidence and mortality. It can in many ways be considered a chronic disease but one requiring considerable surgical care and thus quite costly. We examine several non-invasive measures for diagnostic, staging and prognostic evaluations.

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1 INTRODUCTION[1]

Diagnosing cancers is all too often a challenge. In a recent article in the Wall Street Journal, an Oncologist bemoans the fact that medicine has made little progress in this effort and worse the means and methods of treating the more advanced forms is still archaic and brutal[2]. The author specifically argues[3]:

What we need now is a paradigm shift. Today, the newest methods generating the most research and expense tend to be focused on treating the worst cases—chasing after the last cancer cells in end-stage patients whose prognoses are the worst. We need instead to commit to anticipating, finding and destroying the first cancer cells. We must reliably detect the faint footprints of cancer at the beginning and stop it in its tracks.

Such prevention represents the cheapest, fastest and safest alternative to the terrible, longstanding treatment trio of slash, poison and burn. It's the most universally applicable way to save lives, and the estimated cost-savings from early diagnosis add up to over $26 billion a year, more than any other new approach can promise. Earlier detection is also the most humane way to improve cancer outcomes. Status quo treatments—the combination of surgery, chemotherapy and radiation for solid tumors, or chemo and bone marrow transplants for liquid ones—can be brutal and indiscriminate killers. Treatments often leave patients in agony, while providing mere months of added survival. The new immunotherapies can be even more.

The author's construct of the faint footprints is compelling but alas a distant goal. We simply cannot test everyone for everything. Various Government bodies bemoan using the PSA test for prostate cancer while allowing massive usage of mamographies and identifying numerous DCIS yet denying PSA testing. Many Internists may miss the most obvious of melanomas while identifying various cardiac arrythmias.

We have previously discussed the issue of just what is a cancer. We used PCa and thyroid cancers as examples. Thyroid cancers, especially microcarcinomas are small collections of ill formed cells showing certain aberrant nuclear formations. Yet there is no evidence that they would ever metastasize. HGPIN in the prostate has the ability to just disappear rather than progress. Bladder tumors are often CIS, and may be evident due to small hematuria.

These may all lead to highly invasive tests and even more invasive and putatively morbid surgeries. Thus, despite the authors plea, many of these putative cancers are all too often

[1] This report is written in support of the investigations of Dr. Helena Vila Reyes at Columbia University Medical Center. It presents the opinions solely of the author and is DRAFT and subject to significant change. The report is solely the author's opinions and in no way reflects upon Dr. Reyes' work which may differ from or support the observations herein.

[2] See Raza, We Need a New Start, WSJ, Oct 4, 2019.

[3] https://www.wsj.com/articles/cancer-is-still-beating-uswe-need-a-new-start-11570206319

remedied by the patient's own immune system. On the other hand, the same immune system may be used against the patient to protect and nourish the ever-growing lesion. Perhaps there is no simple answer. Indeed, in cancers there are too often no simple answers.

We examine herein some of these issued as focused on bladder cancer, BCa, a malignancy which is on the on hand complex, and on the other all too often a chronic disease.

Bladder cancer is a malignancy of parts of the bladder. It is not as common as prostate yet can be costly to treat because of ongoing recurrence. As NCBI notes[4]:

Bladder cancer is a disease in which certain cells in the bladder become abnormal and multiply without control or order. The bladder is a hollow, muscular organ in the lower abdomen that stores urine until it is ready to be excreted from the body. The most common type of bladder cancer begins in cells lining the inside of the bladder and is called transitional cell carcinoma (TCC). Bladder cancer may cause blood in the urine, pain during urination, frequent urination, or the feeling that one needs to urinate without results. These signs and symptoms are not specific to bladder cancer, however. They also can be caused by noncancerous conditions such as infections.

Currently the diagnosis of bladder cancer is performed by a cystoscopic exam, excision of tissue, and histo-pathological examination. There is now a proliferation of extensive imaging technologies which arguably provide alternatives to such a process. We examine some of these modalities herein and look at them in the context specifically of bladder cancer.

Our prime question examined herein is:

CAN IMAGING MODALITIES, ESPECIALLY MPMRI, BE USED AS AN ADJUNCT IN STAGING BLADDER CANCER? FURTHERMORE, CAN MPMRI BE USED IN PLACE OF INVASIVE PATHOLOGICAL STUDIES IN DIAGNOSING, STAGING AND PROGNOSTIC EVALUATION OF BLADDER CANCER?

We use existing literature to consider this issue. Specifically, we examine:

1. The current understanding of bladder cancer, BCa, and how it is diagnosed, staged and treated. These are generally histo-pathologic measures of cell structure, morphology, and aggregates of cells as well as some immunohistological measures.

2. The underlying measures which can be obtained non-invasively that reflect the existence of BCa with such samples as miRNA, proteins, DNA, and other exomic measures.

3. The target genetic changes which relate to the initiation and progression of BCa.

4. The use of a multiplicity of imaging modalities which assist in diagnosis

[4] https://www.ncbi.nlm.nih.gov/medgen/14150

5. The specific use of mpMRI, using multiple MRI modalities, to assess their ability to non-invasively diagnose, stage, and give prognostic data.

6. A discussion of a multiplicity of related issues including the putative application of AI.

1 BASICS

We commence with some basic issues regarding bladder cancer, BCa.

1.1 INCIDENCE

NCI notes[5]:

Number of New Cases and Deaths per 100,000: The number of new cases of bladder cancer was 20.1 per 100,000 men and women per year. The number of deaths was 4.4 per 100,000 men and women per year. These rates are age-adjusted and based on 2012-2016 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 2.4 percent of men and women will be diagnosed with bladder cancer at some point during their lifetime, based on 2014-2016 data.

Prevalence of This Cancer: In 2016, there were an estimated 699,450 people living with bladder cancer in the United States.

1.2 CHARACTERIZATIONS

From Goldman's Cecil:

A spectrum of tumors arise from the urothelial lining of the bladder, renal pelvis, ureters, and urethra, of which transitional cell carcinoma is the most common. Most tumors arise from the bladder, with a minority arising from the upper tracts (renal pelvis and ureters) and even fewer from the proximal urethra. Although transitional cell cancers possess a variable natural history, they have a proclivity for multifocality, high recurrence rates, and progression to higher pathologic stages.

*These tumors are generally grouped into the t**hree broad categories of superficial, muscle-invasive, and metastatic disease**, each of which differs in clinical behavior, prognosis, and primary management. For superficial tumors, the aim is to prevent recurrences and progression to a more advanced stage. In muscle-invasive disease, the medical challenge is to integrate the modalities of surgery, chemotherapy, and radiation to optimize cure and minimize morbidity. For metastatic disease, chemotherapy is used to palliate the symptoms of most patients, but there is a subset of patients in whom combination chemotherapy may result in long-term cure.*

1.3 STAGING

From NCI we have the following[6]:

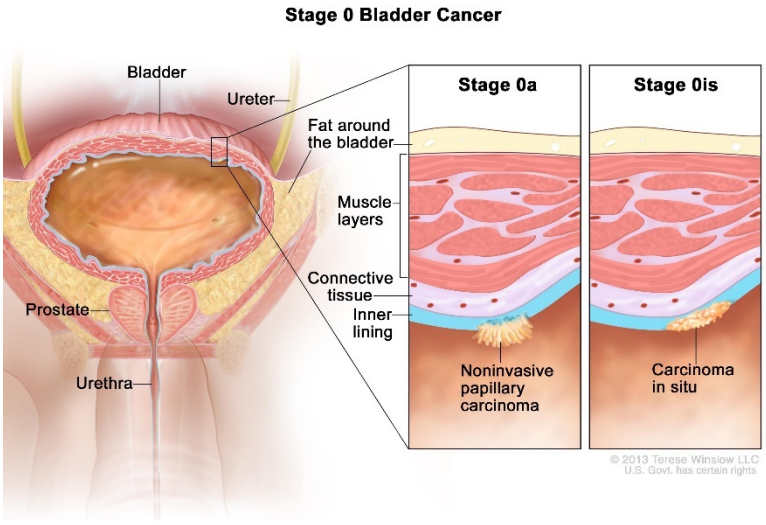
[5] https://seer.cancer.gov/statfacts/html/urinb.html

[6] https://www.cancer.gov/types/bladder/patient/bladder-treatment-pdq

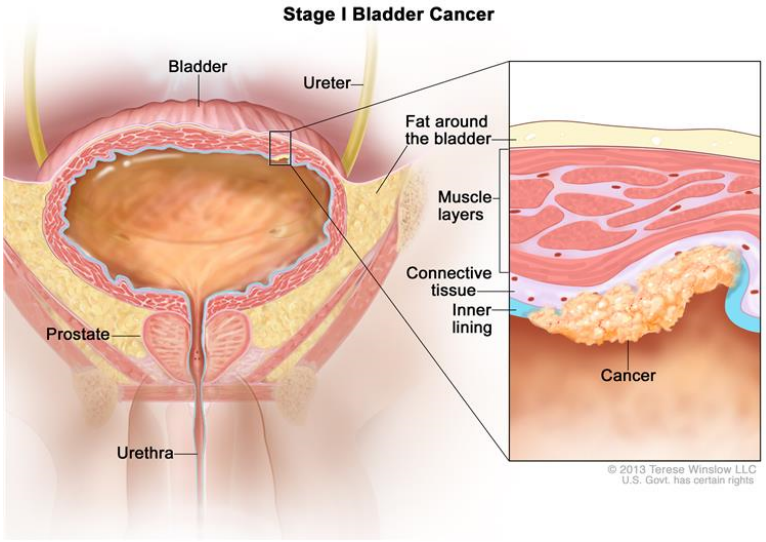
In stage 0, abnormal cells are found in tissue lining the inside of the bladder. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is divided into stages 0a and 0is, depending on the type of the tumor:

Stage 0a is also called noninvasive papillary carcinoma, which may look like long, thin growths growing from the lining of the bladder.

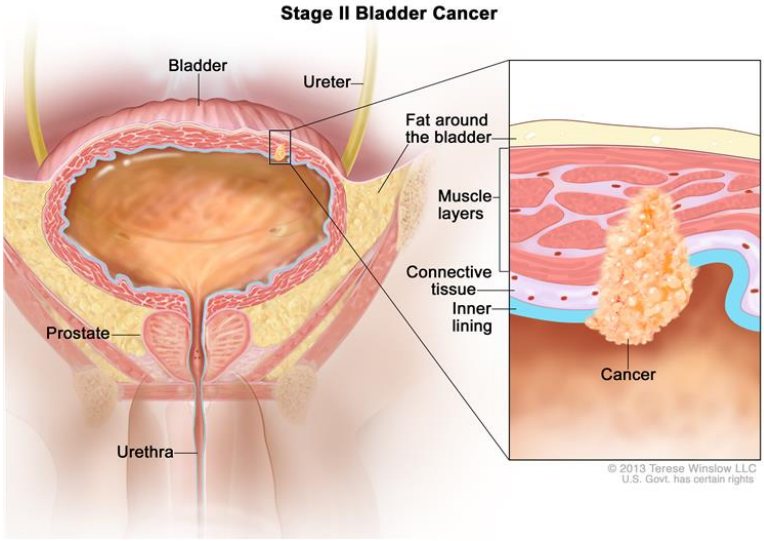
Stage 0is is also called carcinoma in situ, which is a flat tumor on the tissue lining the inside of the bladder.



In stage I, cancer has formed and spread to the layer of connective tissue next to the inner lining of the bladder.



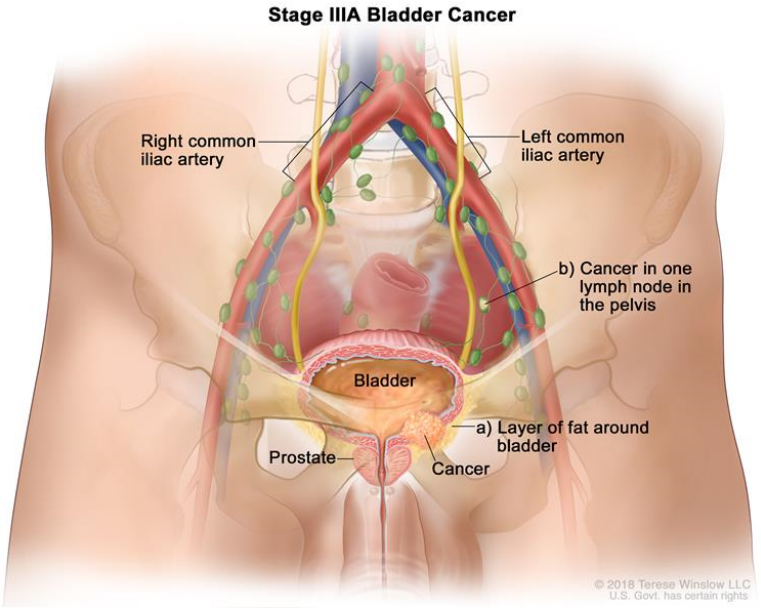
In stage II, cancer has spread to the layers of muscle tissue of the bladder.



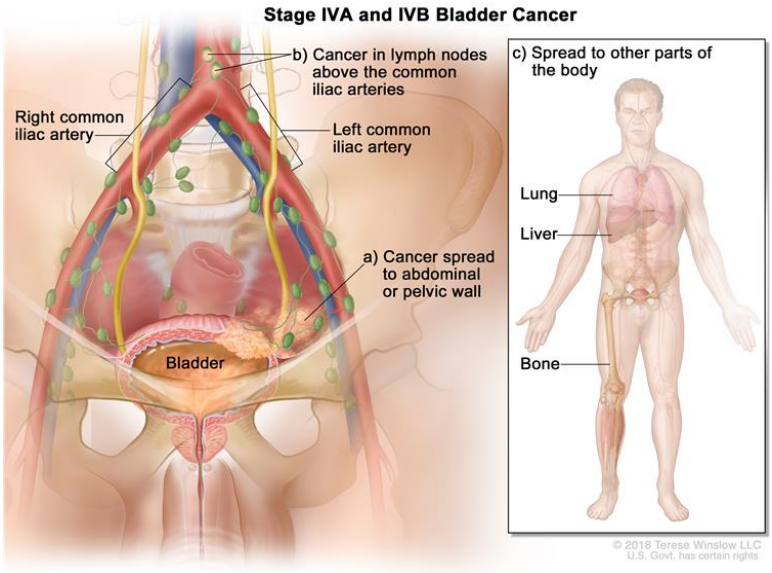
Stage III is divided into stages IIIA and IIIB.

In stage IIIA: cancer has spread from the bladder to the layer of fat surrounding the bladder and may have spread to the reproductive organs (prostate, seminal vesicles, uterus, or vagina) and cancer has not spread to lymph nodes; or cancer has spread from the bladder to one lymph node in the pelvis that is not near the common iliac arteries (major arteries in the pelvis).

In stage IIIB, cancer has spread from the bladder to more than one lymph node in the pelvis that is not near the common iliac arteries or to at least one lymph node that is near the common iliac arteries.



Stage IV is divided into stages IVA and IVB. In stage IVA, cancer has spread (1) from the bladder to the wall of the abdomen or pelvis; or (2) to lymph nodes that are above the common iliac arteries (major arteries in the pelvis). In stage IVB, cancer has spread to other parts of the body, such as the lung, bone, or liver.



1.4 DIAGNOSIS

Returning to our initial discussion; diagnosis. How does one best diagnose bladder cancer? When does such a diagnosis occur? Typically the disease occurs in an older individual, males more frequently than females, and smokers more often than not. The usual sign is blood seen in the urine, or blood found in a routine of incidental urinalysis. Then a cystoscopy is performed using a rigid or flexible scope, and some obvious cells may be removed and sent to a pathologist. If found to be malignant, an issue which we will review in a bit, the process of reduction or elimination ensues.

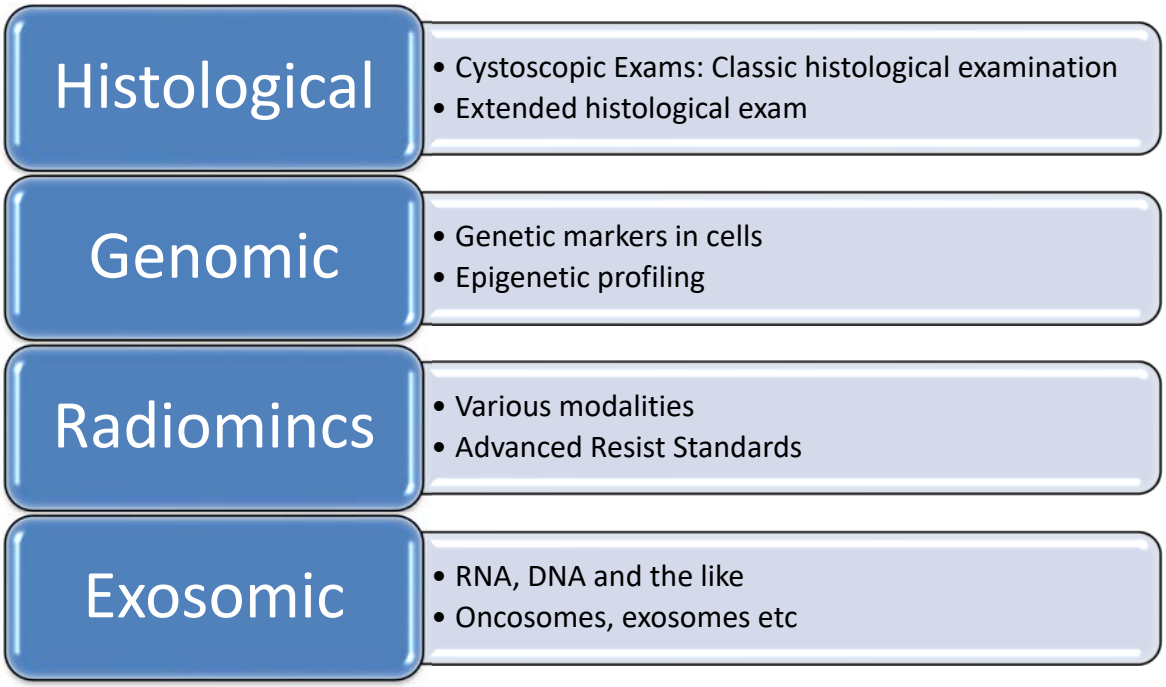
However, one may ask if there are other techniques, less invasive. Also, to follow our introduction, must we wait for symptoms of overt bleeding or are there other markers? Furthermore, if we suspect a BCa, we stage it more effectively without significant surgical intervention?

1.5 ISSUES

There are many issues worth considering. In this report we focus primarily on early detection and not on prognosis or treatment. There is an assortment of detection methodologies, histological examination being the current gold standard. However, histological examination is invasive and not dispositive. One may miss areas, sample lesions only of marginal depth, collect inadequate enough samples and the like.

Furthermore, one may find "cancerous" lesions which is not examined at that time could readily regress, due to immune responses or otherwise. Namely, we are always faced with the question: when is a cancer a cancer[7]?

[7] https://www.researchgate.net/publication/334947163_What_is_Meant_by_Cancer


Histological
• Cystoscopic Exams: Classic histological examination
• Extended histological exam
Genomic
• Genetic markers in cells
• Epigenetic profiling
Radiomincs
• Various modalities
• Advanced Resist Standards
Exosomic
• RNA, DNA and the like
• Oncosomes, exosomes etc

2 PATHOLOGY AND HISTOLOGY

We now briefly detail some of the specifics of BCa.

2.1 ANATOMY

From Gartner and Hiatt, we have the general anatomical description:

The urinary bladder is essentially an organ for storing urine until the pressure becomes sufficient to induce the urge for micturition, or voiding. Its mucosa also acts as an osmotic barrier between the urine and the lamina propria. The mucosa of the bladder is arranged in numerous folds, which disappear when the bladder becomes distended with urine.

During distention, the large, round, dome-shaped cells of the transitional epithelium become stretched and change their morphology to become flattened. The accommodation of cell shape is performed by a unique feature of the transitional epithelial cell plasmalemma, which is composed of a mosaic of specialized, rigid, thickened regions, plaques, interspersed by normal cell membrane, interplaque regions.

When the bladder is empty, the plaque regions are folded into irregular, angular contours, which disappear when the cell becomes stretched. These rigid plaque regions, anchored to intracytoplasmic filaments, resemble gap junctions, but this similarity is only superficial.

Plaques appear to be impermeable to water and salts; thus these cells act as osmotic barriers between the urine and the underlying lamina propria. The superficial cells of the transitional epithelium are held together by desmosomes and, possibly, by tight junctions, which also aid in the establishment of the osmotic barrier by preventing the passage of fluid between the cells.

The triangular region of the bladder, whose apices are the orifices of the two ureters and the urethra, is known as the trigone. The mucosa of the trigone is always smooth and is never thrown into folds. The embryonic origin of the trigone differs from that of the remainder of the bladder.

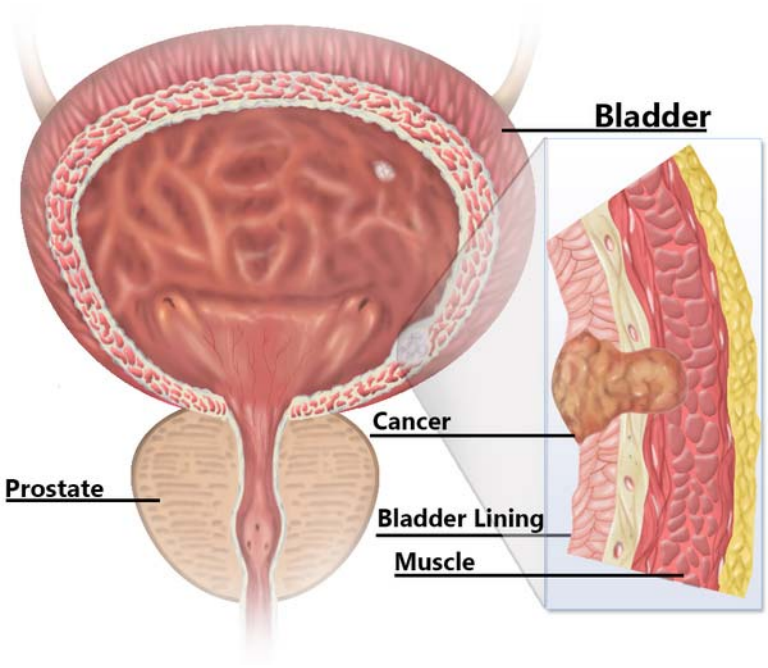
The lamina propria of the bladder may be subdivided into two layers: a more superficial, dense, irregular collagenous connective tissue and a deeper, looser layer of connective tissue composed of a mixture of collagen and elastic fibers. The lamina propria contains no glands except at the region surrounding the urethral orifice, where mucous glands may be found. Usually, these glands extend only into the superficial layer of the lamina propria. They secrete a clear viscous fluid that apparently lubricates the urethral orifice.

The muscular coat of the urinary bladder is composed of ***three interlaced layers of smooth muscle, which can be separated only in the region of the neck of the bladder****. Here, they are arranged as a* ***thin inner longitudinal layer, a thick middle circular layer, and a thin outer***

longitudinal layer. *The middle circular layer forms the internal sphincter muscle around the internal orifice of the urethra.*

The adventitia of the bladder is composed of a dense, irregular collagenous type of connective tissue containing a generous amount of elastic fibers. Certain regions of the adventitia are covered by a serosa, a peritoneal reflection onto the wall of the bladder, whereas other regions may be surrounded by fat.

From the NIH site[8]:



2.2 TYPES

From Goldman's Cecil:

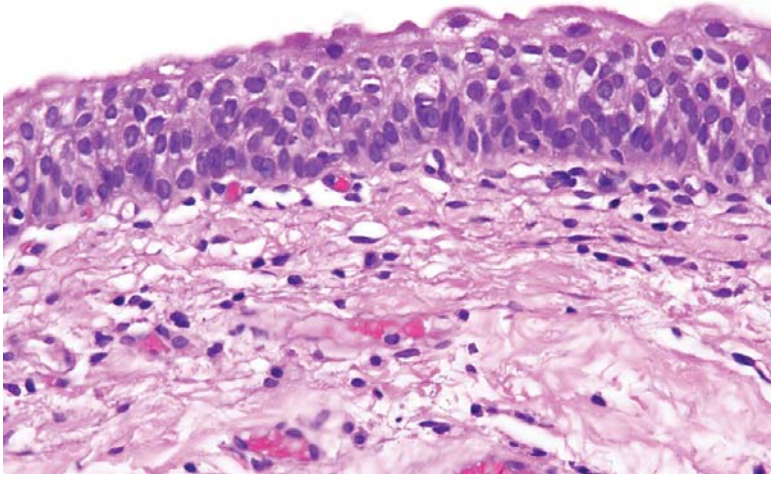
Most (70 to 80%) newly detected bladder cancers are classified as superficial tumors and include exophytic papillary tumors confined to the mucosa (Ta), tumors invading the lamina propria (Tl), and carcinoma in situ (as, also called Tis). Superficial bladder tumors are typically graded according to the World Health Organization International Society of Urologic Pathology (WHOISUP) grading system as low or high grade. If the grading system is not specified, a numerical system can be used: well differentiated (Gl), moderately differentiated (G2), poorly differentiated (G3), and undifferentiated (G4).

[8] https://ghr.nlm.nih.gov/condition/bladder-cancer

Grading is more important for noninvasive Ta tumors because almost all invasive bladder tumors (Tl or greater) are high grade. Primary CIS (or Tis) without a concurrent Ta or Tl tumor constitutes 1 to 2% of new bladder cancer cases. More frequently, CIS is found in the presence of multiple papillary tumors, either immediately adjacent to another lesion or involving remote mucosa in the bladder. CIS is, by definition, high-grade disease; it is regarded as a precursor to more invasive tirmors because 60% of untreated tumors develop more invasive disease within 5 years. ATI tumor is an aggressive, invasive malignancy. Virtually all Tl tumors are high grade, and 50% have associated as. Fifty percent of patients have disease recurrence by 1 year, and 90% within 5 years. A minority of primary tumors at diagnosis are found to invade the muscularis propria (T2), extend to perivesicular fat (T3), or extend into immediately adjacent organs (T4); all primary tumors stage T2 or higher are high grade.

2.3 HISTOLOGY

The histology of the bladder is somewhat standard with a deep epithelial layer and the three underlying layers, the middle being the muscle layer. A sample of a normal bladder from Epstein is shown below. There is a maximum of seven cells in the top epithelial like layer. As a note, cell size may be 10-30 microns so the top layer may be up to 210 microns thick. This will be a critical factor in examining MRI thickness measures.



The epithelial layers are threefold; top umbrella cells lying flat and covering multiple cells below, a middle region, and a basal layer. The epithelial layer is up to seven cells deep. Below that are the muscle layers. There also may from time to time appear fat deposits of varying significance.

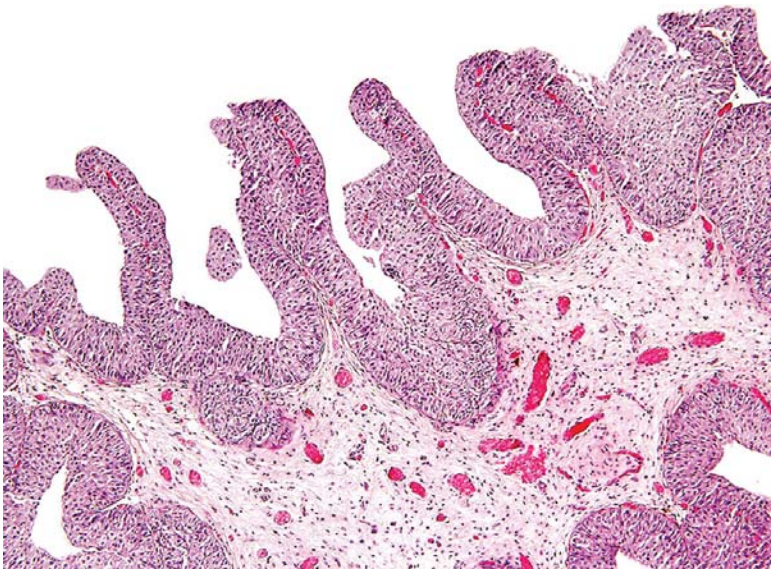
Typical histologic parameters are:

i. Thickness of urothelium

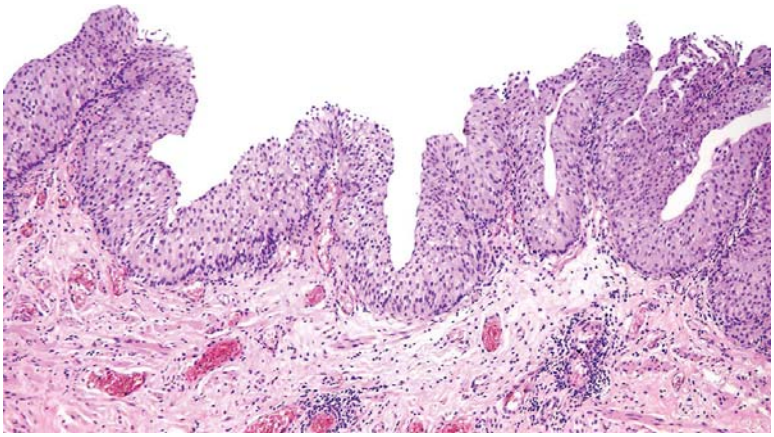
ii. Polarity
iii. Cytoplasmic clearing
iv. Nuclear size
v. Nuclear crowding
vi. Nuclear borders including notches
vii. Nuclear chromatin distribution
viii. Nucleoli
ix. Mitoses including atypical forms
x. Accompanying inflammation
xi. Neovascularity and inflammation at the base of the lesion

In atypia we look for the same factors.

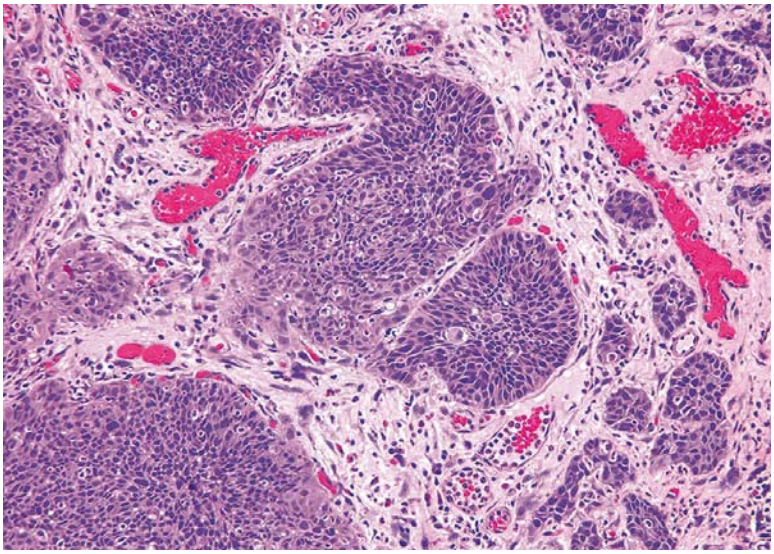
Malignant cells often have a papilla like shape as we show below. Most of the initial malignancies are epithelial and only as the growth continue does it invade the muscle and then metastasize from there.



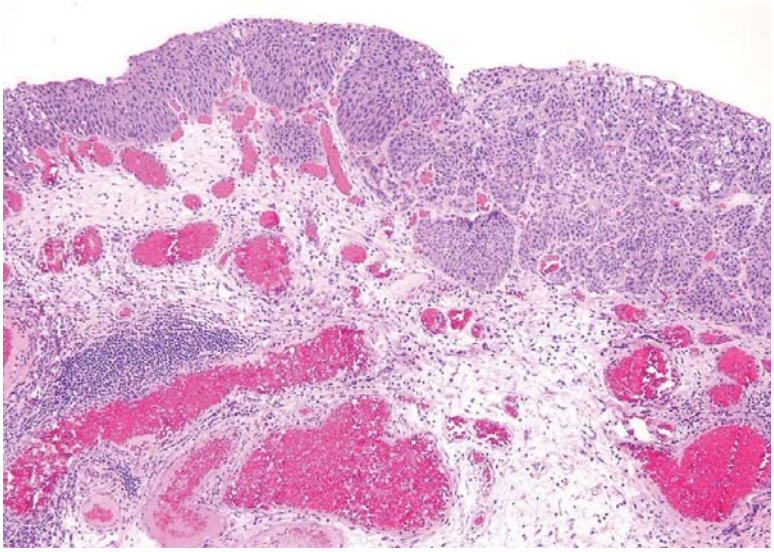
The following is another example of the papillary growth.



An invasive slide below demonstrates the pleomorphism as well as the increased cytoplasm in nests of urothelial carcinoma (from Epstein Fig 5.1)



An example of the lamina propria invasion also from Epstein is below:



The issue here is the complexity of large lesions and the subtlety of the smaller. However can mpMRI as we will discuss have the capability to ascertain these characteristics? As Epstein notes, diagnosis of lamina propria is often quite difficult even with good histological samples. This means that even with all the details on the path slides a good pathologist may have levels of uncertainty. Thus these dimensions may be totally lacking in an mpMRI analysis.

Staging is described as below[9]. However these staging characteristics cannot be adequately achieved by mpMRI as we shall note. Thus there may by necessity have to be developed similar metrics if possible.

Stage	Characterization
CIS (also called Tis)	Flat, high grade, cancer cells are only present in the innermost layer of the bladder lining.
Ta	The cancer is just in the innermost layer of the bladder lining
T1	The cancer has started to grow into the connective tissue beneath the bladder lining
T2	The cancer has grown through the connective tissue into the muscle
T2a	The cancer has grown into the superficial muscle
T2b	The cancer has grown into the deeper muscle
T3	The cancer has grown through the muscle into the fat layer
T3a	The cancer in the fat layer can only be seen under a microscope
T3b	The cancer in the fat layer can be seen on tests, or felt by a doctor during an examination under anesthetic
T4	The cancer has spread outside the bladder
T4a	The cancer has spread to the prostate, womb (uterus), or vagina
T4b	The cancer has spread to the wall of the pelvis or abdomen

[9] https://www.ncbi.nlm.nih.gov/books/NBK330459/table/introduction.t1/

Many of the cancers are of a local nature but have the tendency to arise again and again within the bladder. It is the persistent growth characteristic which make bladder cancer in its chronic state a costly cancer to treat.

3 EXOSOMES ETC.: BLOOD AND URINE

Tumors have the tendency to emit a variety of blood and urine borne markers which can be used to detect the cancer before it has had the chance to spread[10]. Some of these markers have high specificity and sensitivity. We call this the exomic focus as contrast to genomics. Exomics is the study of what the cancer cell sloughs off into the various bodily circulations. Genomics as we use it is the study of the genetic profile of the cells themselves.

We examine the exomic as well as related genomics here. As Bax et al have noted:

Bladder Cancer Bladder cancer (BlC) is the seventh most common cancer and ninth leading cause of cancerrelated death, with an estimated 549,000 new cases and 200,000 deaths in 2018 worldwide. Bladder cancer is more common in men than women, with respective incidence and mortality rates of 9.6 and 3.2 per 100,000 in men: about 4 times those of women globally. Incidence rates in both sexes are highest in Southern Europe (Greece, Spain, Italy), Western Europe (Belgium and the Netherlands), and Northern America. Considering only women, the highest rates are estimated in Lebanon. At the time of diagnosis, about 70–80% of BlC are non-muscle-invasive bladder cancers (NMIBC), while the remaining 20–30% are muscle-invasive bladder cancers (MIBC). Although NMIBC and MIBC both originate from the urothelium in the urinary bladder, they have distinct clinical characteristics.

NMIBC is associated with good survival compared to other malignancies, although 30–50% of patients with NMIBC will eventually experience recurrence after transurethral resection (TUR) of the primary tumor, and 10–20% will progress to muscle-invasive bladder cancer (MIBC). In the case of MIBC, instead, patients often have poor outcomes despite systemic treatments, although radical cystectomy, radiation therapy, and chemotherapy are considered to be effective therapies.

Therefore, early diagnosis of BlC is essential to properly manage BlC and improve the efficacy of treatments and patients' chances of surviving. The current standard procedure for BlC detection and monitoring tumor progression and recurrence involves urine cytology, cystoscopy, and biopsy [92,93]. Urine cytology allows the detection of cancer or pre-cancer cells through a microscope screening of urine samples. However, its low sensitivity towards low-grade tumors reduces test reliability, although it is a perfect tool for the detection of high-grade bladder cancers.

Cystoscopy, i.e., the endoscopy of bladder via urethra, is an expensive, invasive and painful test, which may easily miss high-grade tumors. Indeed, carcinoma in situ (CIS) looks like red mucosal spots typical of inflammatory lesions and may be confused. Therefore, if an abnormal area is seen during cystoscopy, the patient undergoes biopsy to confirm the diagnosis. Although recent advances in biopsy technology, this exam is not a perfect tool and it may miss especially small tumors. Thus, new diagnostic approaches that will improve the diagnostic accuracy of current

[10] https://www.researchgate.net/publication/331318495_Exosomes_and_Cancer

procedure and the discrimination between non-malignant conditions and MIBC from NMIBC are needed. In recent years, many efforts have been made to develop a non-invasive and less expensive tool for diagnosis, prognosis and monitoring of the treatment efficacy.

For this purpose, different analytical techniques, such as LC-MS, GC-MS, and NMR, have been proposed in the scientific literature for the chemical characterization of urine aimed at the identification of potential markers.

As Ward and Bryan have indicated:

The development of accurate biomarkers for the noninvasive detection of urothelial bladder cancer (UBC) could transform patient pathways by reducing reliance on cystoscopy which is burdensome for patients and expensive for healthcare providers. In addition, the identification of highly prognostic (or even predictive) biomarkers could better guide patient management, and especially for those patients with high-risk non-muscle-invasive bladder cancer (HR-NMIBC) who represent a treatment challenge.

*However, despite decades of intensive research, the need for effective biomarkers for bladder cancer detection and prognostication remains unmet. A small number of soluble urinary protein biomarkers (**NMP22, BTA**) or exfoliated cell tests based on proteins (ImmunoCyt) or aneuploidy (UroVysion) have obtained Food and Drug Administration (FDA) approval but have not been widely adopted due to limited sensitivity and/or specificity. More recently, research studies analysing the DNA in urinary cell pellets for changes in copy number, methylation status and somatic mutations have all shown potential for accurate non-invasive detection of bladder cancer. These tests still require thorough validation*

Overall there are a multiplicity of putative liquid biopsy techniques[11].

3.1 MIRNAS

micro RNAs are small 22 base pair RNAs which we have discussed at length elsewhere[12]. BCa emits many and they can have both specificity and sensitivity. Details profiling of these is still lacking[13]. However, we examine some in detail.

As Larrrea et al have noted:

According to the National Cancer Institute, a biomarker is defined as "a biological molecule found in blood, other body fluids, or tissues that are a sign of a normal or abnormal process, or of a condition or disease."

[11] https://www.researchgate.net/publication/325023533_Liquid_Biopsy_and_Cancer

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

[13] https://www.researchgate.net/publication/325046881_PCa_mir34_p53_MET_and_Methylation

In cancer, they can be divided into three general categories:

diagnostic biomarkers, which are used for a differential diagnosis;

prognostic biomarkers, which can distinguish tumors with a good outcome from those with a bad outcome; and

predictive biomarkers, which are for assessing whether a treatment is likely to be effective for a particular patient or not.

An ideal biomarker should have a high specificity, sensitivity, and predictive power. miRNAs have a number of intrinsic characteristics that make them attractive as biomarkers.

Firstly, they are highly specific, and it has been shown that miRNA expression profiles differ between cancer types according to diagnosis and the developmental stage of the tumor, with a greater resolution than traditional gene expression analysis.

Secondly, unlike other RNA classes, miRNAs are remarkably stable and therefore can be robustly measured not only in biological fluids but also from routinely prepared formalin-fixed paraffin-embedded (FFPE) material.

Thus the miRNAs are excellent markers. As we shall note, there are many observed but like many of these markers we have specificity and sensitivity issues.

Indeed, unlike other RNA species, miRNAs appear resistant to boiling, pH changes, repeated freeze-thawing cycles, and fragmentation by chemical or enzymes. It should be noted, however, that cfmiRNAs are not themselves intrinsically resilient to RNase or any other treatment; rather, they are protected by their lipidic or protein-based carrier. As a result of these characteristics, the use of cfmiRNAs as biomarkers—and in particular as cancer biomarkers—has generated a plethora of publications over the last few years.

Due to the limitations of space, we will not attempt to review all of these but instead discuss the more robust studies that identify common cfmiRNA biomarkers in multiple studies. More often than not, these biomarker miRNAs are themselves intimately involved in cancer pathology,…, which includes their respective experimentally validated targets. While it may be tempting to speculate that these miRNAs may have the same effect while in circulation as intracellularly, there is no evidence that this is indeed the case.

The authors continue with the following table;

miRNA	Cancer	Type Biomarker	Body Fluid
miR-19a	Bladder	D	Plasma
miR-106b	Bladder	D	Urine
miR-210	Bladder	D, PG	Serum

miRNA	Cancer	Type Biomarker	Body Fluid
		D	Urine

Liu et al have also presented a table of other miRNAs as shown below, which seems quite extensive and frankly a bit unwieldly:

miRNA	Regulation	Source
miR-21	up	urine & BC cells lines
miR-200c	up	urine
miR-23b	up	urine
miR-513b-5p	up	urine
miR-183	up	urine
miR-205	up	from IBC patients
miR-16-1-3p, miR-28-5p, miR-92a-2-5p, miR-142-3p,		
miR-195-3p, miR-196b-5p, miR-299-3p, miR-492, miR-601, miR-619-5p, miR-3155a, miR-3162-5p, miR-3678-3p, miR-4283,	up	urine
miR-4295, miR-4311, miR-4531, miR-5096, miR-5187-5p		
miR-155-5p, miR-132-3p, miR-31-5p, miR-15a-5p	up	urine
miR-93, miR-940	up	urine
miR-16, miR-96	up	urine
miR-1, miR-99a, miR-125b, miR-133b, miR-143, miR-1207-5p	down	urine
let-7f-2-3p, miR-520c-3p, miR-4783-5p	down	urine
miR-30c-2-5p, miR-30a-5p	down	urine
miR-30a-5p, miR-30c-2-5p, miR-10b-5p	down	urine
miR-30a-5p, let-7c-5p	down	urine
miR-27b-3p	down	BC cells
miR-let-7i-3p	down	BC cells
miR-29c-5p, miR-146b-5p, miR-200a-3p, miR-200b-3p, miR-141-3p	down	BC cells

From Enokida et al we have the following list of miRNAs and their gene targets:

miRNA	Type (TS, tumor suppressor, ONC oncogenic)	Target Gene
miR-1	TS	LASP1
		PNP
		PTMA

miRNA	Type (TS, tumor suppressor, ONC oncogenic)	Target Gene
		SRSF9
		TAGLN2
miR-16	TS	CCND1
miR-23b	TS	EGFR
		MET
		ZEB1
miR-24	TS	CARD10
		FOXM1
miR-27a	TS	RUNX1
		SLC7A11
miR-27b	TS	DROSHA
		EGFR
		MET
miR-29c	TS	CDK6
miR-30a	TS	NOTCH1
miR-34a	TS	CD44
		HNF4G
		NOTCH1
miR-99a	TS	FGFR3
miR-100	TS	MTOR
miR-101	TS	COX2
		MET
		VEGFC
miR-124-3p	TS	ROCK1
		CDK4
miR-125b	TS	E2F3
		MMP13
		SPHK1
miR-128	TS	VEGFC
miR-129	TS	GALNT1
		SOX4
miR-133a	TS	EGFR
		FSCN1
		GSTP1
		LASP1

miRNA	Type (TS, tumor suppressor, ONC oncogenic)	Target Gene
		PNP
		PTMA
		TAGLN2
miR-133b	TS	AKT1
		BCL2L2
		EGFR
miR-135a	TS	FOXO1
miR-138	TS	ZEB2
miR-143	TS	SERPIN1
		AKT
miR-144-5p/3p	TS	CCNE1
		CCNE2
		CDC25A
		PKMYT1
miR-145	TS	CBFB
		CLINT1
		FSCN1
		ILK
		PAK1
		PPP3CA
		SERPIN1
		SOCS7
		IGF1R
miR-186	TS	HMGN5
miR-193a-3p	TS	LOXL4
		PSEN1
		HOXC9
miR-195	TS	BIRC5
		CDC42
		CDK4
		GLUT3
		WNT7A
miR-200b	TS	MMP16
miR-200c	TS	BMI1
		E2F3

miRNA	Type (TS, tumor suppressor, ONC oncogenic)	Target Gene
miR-203	TS	BCL2L2
		BIRC5
miR-214	TS	PDRG1
miR-218	TS	BMI1
		LASP1
miR-221	TS	STMN1
miR-320a	TS	ITGB3
miR-320c	TS	CDK6
miR-449a	TS	CDC25A
miR-485-5p	TS	HMGA2
miR-490-5p	TS	FOS
miR-493	TS	FZD4
		RHOC
miR-497	TS	BIRC5
		WNT7A
miR-574-3p	TS	MESDC1
miR-576-3p	TS	CCND1
miR-590-3p	TS	TFAM
miR-1182	TS	TERT
miR-9	Onco	CBX7
		CERS2
miR-10b	Onco	HOXD10 KLF4
miR-19a	Onco	PTEN
miR-96	Onco	CDKN1A
miR-150	Onco	PDCD4
miR-155	Onco	DMTF1
miR-182-5p	Onco	RECK
		SMAD4
miR-708	Onco	CASP2

Thus, there is a large multiplicity and an even larger targeting set. Profiling of these in the context of what is a significant marker and not is yet to be done.

miRNAs have great potential. We have examined them previously but the need to find good targets is still and open question.

3.2 DNAs

As with miRNAs we have DNA fragments as well. From Ward and Bryan:

More recently, research studies analysing the DNA in urinary cell pellets for changes in copy number, methylation status and somatic mutations have all shown potential for accurate non-invasive detection of bladder cancer. These tests still require thorough validation both in the incident and recurrent disease settings. Pitfalls include obtaining sufficient high-quality DNA from all urine samples, dilution of tumour DNA (tDNA) with nontumour DNA, the heterogeneity of bladder cancer and, for surveillance, verifying biomarkers that are absolutely cancer specific, i.e., are not seen in any "field effect"

Method	Disadvantages	Advantages
DNA methylation	Relatively large amount of DNA required Influenced by other factors (age, smoking)	Very high specificity and sensitivity recently reported
Copy number changes	Unable to detect low levels of tumour DNA in a high background of non-tumour DNA	High specificity and most UBCs have copy number changes (10)
Microsatellite analysis	Unable to detect low levels of tumour DNA in a high background of non-tumour DNA Multiple individual tests needed	Good sensitivity and specificity reported
Mutations	Multiple mutations must be analyzed to achieve high sensitivity	High specificity and can detect low levels of tumour DNA in a high background of non-tumour DNA

3.3 PROTEINS

Proteins also are found to be exomics. Both blood and urine contain proteins exuded from cancer cells. Liu et al note the following list of proteins:

Protein ID	Sample Sources
EHD4	urine and BC cells
HEXB	urine and BC cells
ANXA; SND1	urine and BC cells
S100A4	urine and BC cells
TALDO1	urine and BC cells
MUC1	urine and BC cells
EPS8	urine
CEAM5	urine
CD44; BSG	BC cells
ITGB1; ITGA6; CD36; CD73; CD10; CD147; 5T4	BC Cells
NRAS; MUC4	urine
SERPINA1 H2B1K	urine
TACSTD2	urine
EDIL3	urine and BC cells
POSTN	urine and BC cells
CTNNB1; CDC42	urine and BC cells
14-3-3; ALIX; B2M; EGFR; EZR; FSCN1; LGALS; GST; MSN; PRDX1; PTGFRN; RDX; TAGLN2	BC cells

The above is a significant list. Yet, as with miRNAs and other exomics, they have been noted but their specificity and sensitivity are lacking to any great degree.

3.4 GENOMICS

As we noted, genomics is the study of the genetic variations in the tumor cells. We are reaching the point where by cell flow cytometry we can examine the genetic issues on a cell by cell basis. Unlike some cancers, such as thyroid, we do not have cell specific morphological markers such as notched nuclei and clear cytoplasm[14]. From Meeks et al we have the following table listing the most significant genetic alterations:

[14] See, https://www.researchgate.net/publication/335404502_Thyroid_Cancer_and_Genetic_Differentiation , https://www.researchgate.net/publication/334429457_miRNAs_Genes_and_Cancer_Cytology , https://www.researchgate.net/publication/331935614_Thyroid_Cancer_Seek_and_Ye_Shall_Find

Gene Altered	Non progressor	Progressor Baseline	Progressor Muscle Invasive	Metastatic
TERT	10/15 (66%)	7/10 (70%)	5/8 (62%)	9/11 (81%)
TP53	9/15 (60%)	6/10 (60%)	6/8 (75%)	4/11 (36%)
RB1	5/15 (33%)	1/10 (10%)	0/8 (0%)	0/11 (0%)
PIK3CA	6/15 (40%)	3/10 (30%)	2/8 (25%)	4/11 (36%)
PTEN	1/15 (6%)	1/10 (10%)	1/8 (12%)	0/11 (0%)
2D (MLL2)				4/11 (36%)
ARID1A	6/15 (40%)	2/10 (20%)	2/8 (25%)	1/11 (9%)
CDKN2A/B	1/15 (6%)	2/10 (20%)	3/8 (37%)	7/11 (63%)
CCND1 amp	2/15 (12%)	2/10 (20%)	3/8 (37%)	3/11 (27%)
FGFR/FGF	9/15 (60%)	6/10 (60%)	5/8 (62%)	6/11 (54%)

Nothing in the above are surprising given the profile of most somatic cancers. As Vandekerkhove et al note:

*The analysis of **circulating tumor DNA (ctDNA)** in plasma has shed light on the somatic landscape of metastatic disease in several solid malignancies. Prognostic and predictive ctDNAbased biomarkers are beginning to emerge in prostate, colon and pancreatic cancer. In non-small cell lung cancer, a 'companion diagnostic' **ctDNA test for the EGFR T790M mutation** recently received FDA approval.*

However, the abundance and utility of ctDNA in advanced BCa remains largely unexplored, with prior studies limited by small cohort sizes and dependency on single gene sequencing and/or digital droplet PCR (ddPCR) assays to detect specific missense mutations. While ddPCR provides the sensitivity required to detect extremely low levels of ctDNA (e.g. for predicting disease relapse after curative therapy, only broad nextgeneration sequencing assays can deliver a comprehensive analysis of clinically-relevant alterations such as PI3K/mTOR pathway deregulation or somatic hypermutation. In this study we applied a custom sequencing approach to plasma cell-free DNA (cfDNA) collected from a cohort of patients with aggressive BCa. We reveal the landscape of somatic alterations detected across 50 clinically-relevant driver genes in metastatic BCa, demonstrating the promise of liquid biopsies as both a discovery tool and a biomarker for therapy selection. …

Across the 26 patients with quantifiable ctDNA in at least one cfDNA sample (or in two cases, metastatic tissue), we detected 281 somatic mutations including 121 protein altering mutations. We identified 22 missense or truncating mutations in TP53 in 17/26 patients...

The large number of mutations make any identification problematic.

Incorporating copy number results, 24/26 patients carried either a TP53 inactivating change (n=19), RB1 inactivating change (n=8), MDM2 gain (n=2), or CDKN2A loss (n=6), likely resulting in disrupted cell cycle regulation (Figure 3C). For the two patients without alterations in these four genes, E-006 had non-metastatic disease, and BC-008 had a low ctDNA fraction not amenable to copy number analysis.

Four patients exhibited definitive evidence for biallelic inactivation of RB1 or CDKN2A. Over half the cohort (19/26 patients) had mutations or disrupting rearrangements in chromatin modifier genes (Figure 3C), including eight truncating mutations within ARID1A that remove the DNA binding domain and/or glucocorticoid receptor binding domain, and eight truncating mutations in KMT2D (MLL2). TERT promoter mutations were identified in 12/26 patients: ten patients harboured the chr5:1295113:G>A mutation (reported in 65% of BCa), while two carried the chr5:1295135:G>A mutation (reported in 10% of BCa).

The majority of patients had alterations to the PI3K/mTOR pathway, including six with hotspot missense mutations in PIK3CA (K111E, E542K, E545K (n=2), E674Q or E726K), four with truncating mutations in TSC1 (mutually exclusive with PIK3CA hotspot mutations), one with PIK3R1 stopgain, one with PTEN stopgain, and one with a TSC2 truncating rearrangement (Figure 3C). Six patients showed evidence for PTEN or PIK3R1 deletion.

Nine patients (35%) carried ERBB2 activating somatic changes, including amplification in five patients (Supplementary Figure S8), and hotspot mutations (S310F, L755S, I767M, V777L) in four patients. Four patients carried ERBB3 activating alterations, including two amplifications and two hotspot mutations (M91I, V104L) (Figure 3C). Remarkably, one patient had an average of 71 copies ERBB2 in his ctDNA. Three more patients carried activating RAS mutations (KRAS G12D (n=2), HRAS Q61R), and one patient carried a KRAS amplification. In total, 15/26 patients carried activating somatic alterations in the MAPK pathway

We summarize these genes in the following table using reference to NCBI data bases. Also details are in Cantley et al regarding pathways.

Gene Altered	Normal Function
TERT[15]	Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, encoded by this gene, and an RNA component which serves as a template for the telomere repeat. Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres. Deregulation of telomerase expression in somatic cells may be involved in oncogenesis
TP53[16]	This gene encodes a tumor suppressor protein containing transcriptional activation, DNA binding, and oligomerization domains. The encoded protein responds to diverse cellular stresses to regulate expression of target genes, thereby inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Mutations in this gene are associated with a variety of human cancers, including hereditary cancers such as Li-Fraumeni syndrome.
RB1[17]	The protein encoded by this gene is a negative regulator of the cell cycle and was the first tumor suppressor gene found. The encoded protein also stabilizes constitutive heterochromatin to maintain the overall chromatin structure. The active, hypophosphorylated form of the protein binds transcription factor E2F1. Defects in this gene are a cause of childhood cancer retinoblastoma (RB), bladder cancer, and osteogenic sarcoma
PIK3CA[18]	Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by this gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. This gene has been found to be oncogenic and has been implicated in cervical cancers
PTEN[19]	This gene was identified as a tumor suppressor that is mutated in a large number of cancers at high frequency. The protein encoded by this gene is a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It contains a tensin like domain as well as a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. Unlike most of the protein tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates. It negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway. The use of a non-canonical (CUG) upstream initiation site produces a longer isoform that initiates translation with a leucine, and is thought to be preferentially associated with the mitochondrial inner membrane. This longer isoform may help regulate energy metabolism in the mitochondria.
2D (MLL2)[20]	The protein encoded by this gene is a histone methyltransferase that methylates the Lys-4 position of histone H3. The encoded protein is part of a large protein complex called ASCOM, which has been shown to be a transcriptional regulator of the beta-globin and estrogen receptor genes. Mutations in this gene have been shown to be a cause of Kabuki syndrome.

[15] https://www.ncbi.nlm.nih.gov/gene/7015

[16] https://www.ncbi.nlm.nih.gov/gene/7157

[17] https://www.ncbi.nlm.nih.gov/gene/5925

[18] https://www.ncbi.nlm.nih.gov/gene/5290

[19] https://www.ncbi.nlm.nih.gov/gene/5728

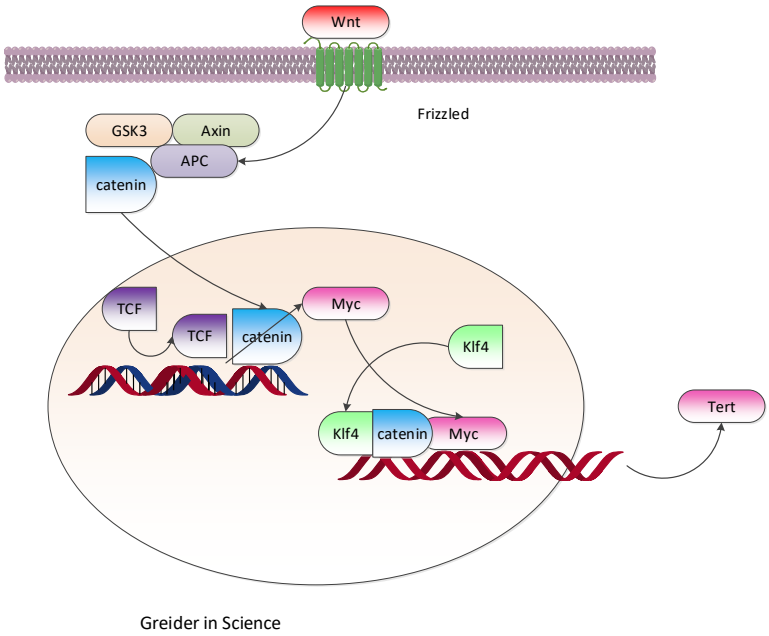
[20] https://www.ncbi.nlm.nih.gov/gene/8085

Gene Altered	Normal Function
ARID1A[21]	This gene encodes a member of the SWI/SNF family, whose members have helicase and ATPase activities and are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. The encoded protein is part of the large ATP-dependent chromatin remodeling complex SNF/SWI, which is required for transcriptional activation of genes normally repressed by chromatin. It possesses at least two conserved domains that could be important for its function. First, it has a DNA-binding domain that can specifically bind an AT-rich DNA sequence known to be recognized by a SNF/SWI complex at the beta-globin locus. Second, the C-terminus of the protein can stimulate glucocorticoid receptor-dependent transcriptional activation. It is thought that the protein encoded by this gene confers specificity to the SNF/SWI complex and may recruit the complex to its targets through either protein-DNA or protein-protein interactions.
CDKN2A/B[22]	This gene generates several transcript variants which differ in their first exons. At least three alternatively spliced variants encoding distinct proteins have been reported, two of which encode structurally related isoforms known to function as inhibitors of CDK4 kinase. The remaining transcript includes an alternate first exon located 20 Kb upstream of the remainder of the gene; this transcript contains an alternate open reading frame (ARF) that specifies a protein which is structurally unrelated to the products of the other variants. This ARF product functions as a stabilizer of the tumor suppressor protein p53 as it can interact with, and sequester, the E3 ubiquitin-protein ligase MDM2, a protein responsible for the degradation of p53. In spite of the structural and functional differences, the CDK inhibitor isoforms and the ARF product encoded by this gene, through the regulatory roles of CDK4 and p53 in cell cycle G1 progression, share a common functionality in cell cycle G1 control. This gene is frequently mutated or deleted in a wide variety of tumors, and is known to be an important tumor suppressor gene.
CCND1[23] **amp**	The protein encoded by this gene belongs to the highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance throughout the cell cycle. Cyclins function as regulators of CDK kinases. Different cyclins exhibit distinct expression and degradation patterns which contribute to the temporal coordination of each mitotic event. This cyclin forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activity is required for cell cycle G1/S transition. This protein has been shown to interact with tumor suppressor protein Rb and the expression of this gene is regulated positively by Rb. Mutations, amplification and overexpression of this gene, which alters cell cycle progression, are observed frequently in a variety of tumors and may contribute to tumorigenesis
FGFR/FGF[24]	This gene encodes a member of the fibroblast growth factor receptor (FGFR) family, with its amino acid sequence being highly conserved between members and among divergent species. FGFR family members differ from one another in their ligand affinities and tissue distribution. A full-length representative protein would consist of an extracellular region, composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment and a cytoplasmic tyrosine kinase domain. The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis and differentiation. This particular family member binds acidic and basic fibroblast growth hormone and plays a role in bone development and maintenance.

We depict some of the key pathways below:

3.4.1 TERT

TERT is associated with the hedgehog pathway as shown below. It is a controller of the telomerase.



3.4.2 FGR

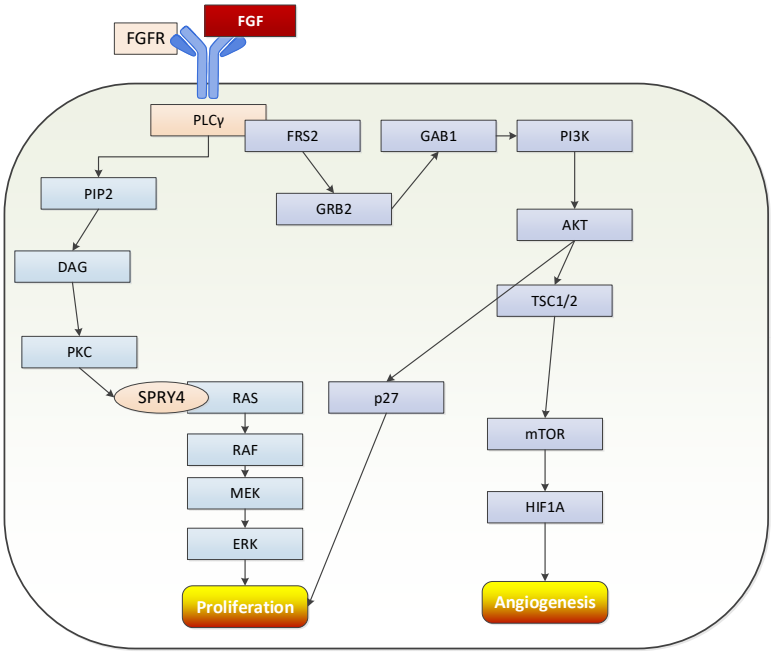
Growth factors and their receptors play a significant role in almost all malignancies[25]. We depict below the FGF complex and the resulting proliferation and angiogenesis that results. FGF and FGFR can be attractive targets across many cancers.

[21] https://www.ncbi.nlm.nih.gov/gene/8289

[22] https://www.ncbi.nlm.nih.gov/gene/1029

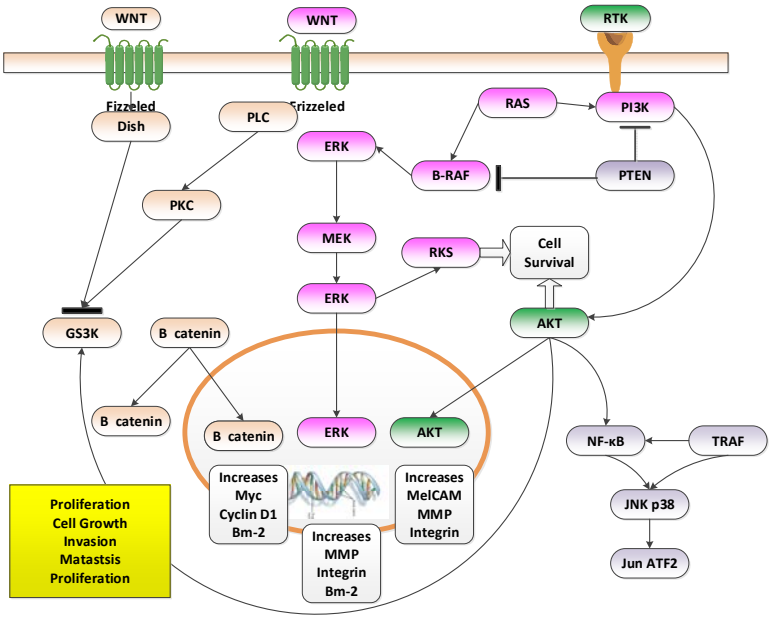
[23] https://www.ncbi.nlm.nih.gov/gene/595

[24] https://www.ncbi.nlm.nih.gov/gene/2261 and
[25] https://www.researchgate.net/publication/329702571_Growth_Factors_Pathways_and_Cancers



3.4.3 PTEN

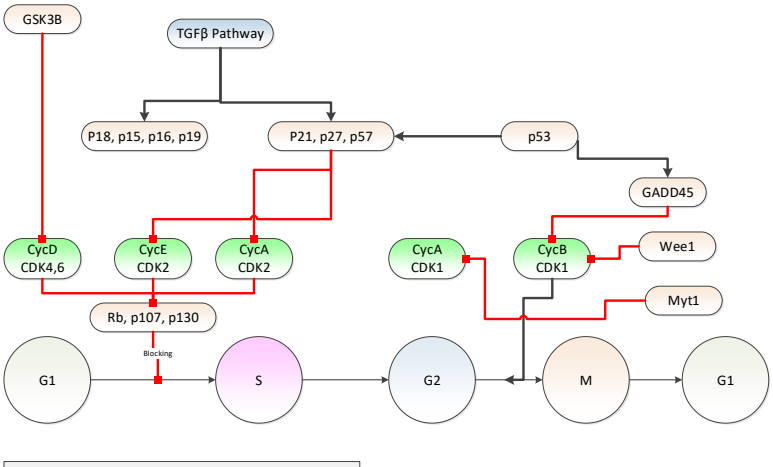
PTEN is a classic gene and protein involved in regulating cells. Loss of PTEN is well known as a cancer inducer in prostate cancer[26].



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

3.4.4 CDKs

Cyclin dependent kinases play a significant role in the cell cycle related to proliferation. We depict them below:



From Solimini et al: "*Known pathways with multiple shRNAs in the validation screen. Genes that validated in the secondary screen by a factor of ≥4 with multiple shRNAs are denoted with circles corresponding to three to five shRNAs (orange) and six or more shRNAs (red).*"

3.5 IMMUNOTHERAPEUTICS

Now from Karp and Falchook we have the following details regarding gene targets and immunotherpeutics.

Target	Abnormality	Prevalence (%)	Clinical Results
PD-1/PD-L1	Expression not needed for activity	Variable	**For second line, platinum failures:** **Pembrolizumab (PD-1** inhibitor) **Nivolumab** (PD-1 inhibitor) **Atezolizumab (PD-L1** inhibitor)
FGFR3	Mutation	20	BGJ398 (FGFR3 inhibitor): **Erdafitinib** (FGFR3 inhibitor)
HRAS	Mutation		**Lonafarnib** (farnesyltransferase inhibitor): **Tipifarnib (R115777)** (farnesyltransferase inhibitor)
PIK3CA	Mutation	20	GSK2126458 (GSK358) (PI3K/MTOR inhibitor): ⋅
TSC1	Mutation	9	
AKT1	Mutation	3	**Everolimus** (mTOR inhibitor): ⋅
PTEN	Mutation	3	MK-2206 (AKT inhibitor)

The immunotherpeutics are one branch and there are also kinase inhibitors and the like.

4 RADIOMICS

Salmanoglu et al have recently presented a summary of various imaging modalities related to bladder cancer. The authors summarize as follows:

For initial diagnosis of BCa, cystoscopy is generally performed. However, cystoscopy cannot accurately detect carcinoma in situ (CIS) and cannot distinguish benign masses from malignant lesions. CT is used in two modes, CT and computed tomographic urography (CTU), both for diagnosis and staging of BCa. However, they cannot differentiate T1 and T2 BCa. MRI is performed to diagnose invasive BCa and can differentiate muscle invasive bladder carcinoma (MIBC) from non-muscle invasive bladder carcinoma (NMIBC).

However, CT and MRI have low sensitivity for nodal staging. For nodal staging PET/CT is preferred. PET/MRI provides better differentiation of normal and pathologic structures as compared with PET/CT. Nonetheless none of the approaches can address all issues related for the management of BCa. Novel imaging methods that target specific biomarkers, image BCa early and accurately, and stage the disease are warranted.

Kumar et al have discussed the issue as follows:

***"Radiomics"** refers to the extraction and analysis of large amounts of advanced quantitative imaging features with high throughput from medical images obtained with computed tomography (CT), positron emission tomography (PET) or magnetic resonance imaging (MRI). Importantly, these data are designed to be extracted from standard-of-care images, leading to a very large potential subject pool.*

Radiomic data are in a mineable form that can be used to build descriptive and predictive models relating image features to phenotypes or gene-protein signatures. The core hypothesis of radiomics is that these models, which can include biological or medical data, can provide valuable diagnostic, prognostic or predictive information.

The radiomics enterprise can be divided into distinct processes, each with its own challenges that need to be overcome:

(i) image acquisition and reconstruction

(ii) image segmentation and rendering

(iii) feature extraction and feature qualification

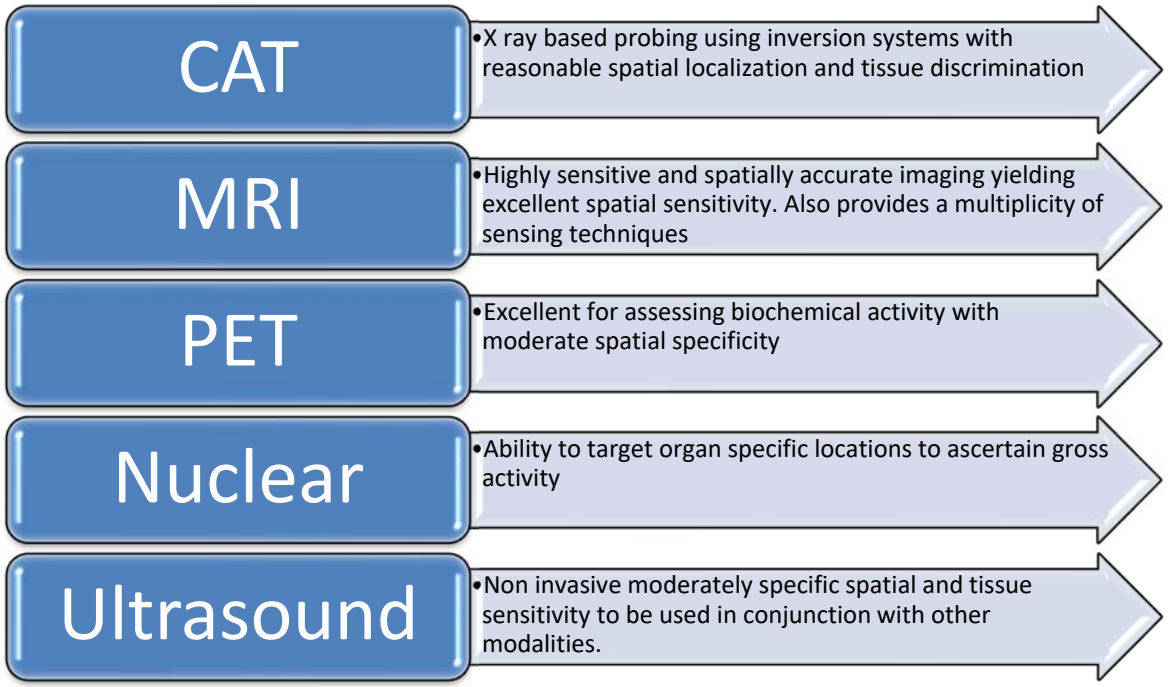
(iv) databases and data sharing for eventual

(v) ad hoc informatic analyses.

Each of these individual processes poses unique challenges. For example, optimum protocols for image acquisition and reconstruction have to be identified and harmonized. Also, segmentations have to be robust and involve minimal operator input. Features have to be generated that robustly reflect the complexity of the individual volumes, but cannot be overly complex or redundant. Furthermore, informatics databases that allow incorporation of image features and image annotations, along with medical and genetic data have to be generated.

Finally, the statistical approaches to analyze these data have to be optimized, as radiomics is not a mature field of study. Each of these processes will be discussed in turn, as well as some of their unique challenges and proposed approaches to solve them. The focus of this article will be on images of non-small cell lung cancer, NSCLC

We examine several imaging modalities as noted below:



4.1 CT

CT, computer assisted tomography, is a standard ionizing form of tomographic analysis which can yield excellent 2D and 3D imaging. It has the disadvantage of high X ray exposure as well as less than excellent resolution. As Salmanoglu et al note:

CT is faster and more cost-effective than MRI, but it is associated with the risk of ionizing radiation, high interobserver variability, and can neither differentiate bladder wall muscle layers, nor can it reliably distinguish T1 from T2 disease. Furthermore, its specificity and sensitivity are low for extravesical extension of early stage BCa and small metastatic lesions of BCa. Dual energy spectral CT is a relatively new method that provides multiparametric imaging

of the urinary system. On the monochromatic images, a threshold value of 73.4 Hounsfield unit demonstrated high sensitivity (77.0%) and specificity (82.5%) for differentiating posterior wall BCa from benign prostate hypertrophy.

Bagheri et al further note:

In the last few years, a major advance in cancer has been improved multidetector CT acquisition quality with reduced radiation exposure, thanks to model-based iterative reconstruction and other dose-reduction initiatives. Processing speeds finally allow for real-time noise reduction to make up for reduced exposures. CT can detect UC in the bladder with a sensitivity of 79%–89.7% and specificity of 91%–94.7%. Before patients undergo radical cystectomy, a contrast-enhanced CT or MRI scan is taken to assess local/ regional tumor invasion and distant metastases.

In MIBC and high-grade non-muscle invasive bladder cancer (NMIBC), CT of the abdomen and pelvis can help to stage and differentiate tumors with transmural spread to the extravesical space from tumors localized to the bladder wall. Furthermore, CT is relatively low-cost, more time-efficient, is often easier and faster to schedule than MRI or PET, and can assess nodal and metastatic stage. Unfortunately, CT is not optimal for accurately determining local extension and early lymph node involvement. Specificity ranges from 68%–100% and does not consistently correlate with pathology because lymph node enlargement can be secondary to other etiologies.

Since the development of CT urography (CTU), IV pyelogram is no longer used in the diagnosis and surveillance of localized urothelial carcinoma of the bladder, ureter, and renal pelvis. Instead, a CT scan of the abdomen with and without contrast with delayed/excretory phase images can carefully assess the collecting system, ureters, and bladder, while evaluating the kidney for parenchymal lesions. The specificity and sensitivity of CTU in identifying the source of hematuria range from 83%–99% and 79%–95%, respectively. Unfortunately, CTU cannot adequately stage the depth of invasion of the primary bladder tumor because it doesn't have the resolution to distinguish between individual layers of the bladder, nor can it distinguish high-risk MIBC from low-grade NMIBC.

In addition, CTU can miss lesions of < 1 cm and carcinoma in situ. When CTU is employed following transurethral resection of bladder tumor (TURBT), inflammatory changes are indistinguishable from tumor extension, reducing the accuracy of local staging to approximately 60%. Also, in patients on surveillance for NMIBC, upper urinary tract surveillance by CTU was inadequate, as only 29% of patients with upper urinary tract disease were diagnosed by routine CTU.

Although CTU is an excellent modality for screening for hematuria and surveillance after NMIBC, it is of limited use in staging primary bladder tumors. However, an increase in bladder wall thickness of > 150% is associated with all-cause and urothelial carcinoma mortality. Furthermore, CTU is only 70%–90% accurate in determining lymph node involvement, and false negative rates range from 25%–40%, likely due to CT's inability to distinguish between inflammatory and tumor-positive lymph nodes.

Nor is CT useful in detecting small (< 1 cm) lymph nodes with microscopic tumors. Overall, the accuracy of pelvic lymph node staging in localized bladder urothelial carcinoma by CT scan is 78%, with sensitivity and specificity ranging from 30%–53% and 94%–98%, respectively. Thus, while CTU has replaced IV pyelogram for diagnosing and staging of urothelial carcinoma of the bladder, it has limitations

4.2 MRI

We now examine MRI modalities which have become more effective in a variety of cancers including bladder and prostate. It is worth a brief review of MRI technology to better understand the potential advantages and options available.

4.2.1 Basic Principles

Let us begin with a brief discussion of how MRI imaging works

1. HYDROGEN ATOMS RESONATE AT A FREQUENCY THAT DEPENDS ON THE MAGNETIC FIELD STRENGTH.

Namely, hydrogen atoms spin and thus have a magnetic moment. In an unmodified environment the spin is random. But if we were to place them in a strong magnetic field they align in the same direction and spin at the same rate or frequency.

2. MAGNETIC FIELD CAN ALIGN RANDOM HYDROGEN ATOMS AND THEN IF WE CHANGE IT SAY 90 DEGREES, WE GET A PULSE AT THE FREQUENCY OF THE LOCAL MAGNETIC FIELD

If we have first aligned the hydrogen atoms in a strong field and then we "pulse" the field so that they change alignment by say 90 degrees and then allowed to realign, the hydrogen atoms emit a signal at the frequency they were at which is called an echo. The echo is a single frequency signal with an amplitude reflective of the density of the emitting material.

3. IF WE CAN CREATE A FIELD GRADIENT THEN THE FREQUENCY REFLECTS A LOCATION RELATIVE TO THE GRADIENT

Remember that the frequency of rotation and of the emitted signal is directly proportional to the field. If we can make the field dependent on the location then the emitted frequency is dependent on the location, and if we can measure the amplitude at each frequency, we have a measure of the sensed volume, a voxel, at each point.

4. WE CAN THEN DO THE ABOVE, COLLECT THE TOTAL COLLECTION OF SIGNALS FROM ALL FREQUENCIES AND USE THIS COLLECTIVE SIGNAL TO PROCESS THE RESULT. WE OBTAIN THE SPATIAL DENSITY BY USING A FOURIER TRANSFORM OF THE SUM OF THE RESONANCES.

We have small receivers surrounding the enclosure and they detect the multiplicity of signals. The signals received are the totality of the echo resonances which have magnitudes reflective of

the density of the resonating materials. Namely in mathematic terms the received signal is the Fourier transform of the image desired. So we can simply take its Fourier transform to get back the spatial image itself. In a sense this is much simpler than the Randon transform used in CAT systems.

5. INVERTING THE DATA GIVES MEASURE IN 2 DIMENSIONAL SPACE OF THE HYDROGEN DENSITY OF THE GRID MADE BY THE GRADIENTS

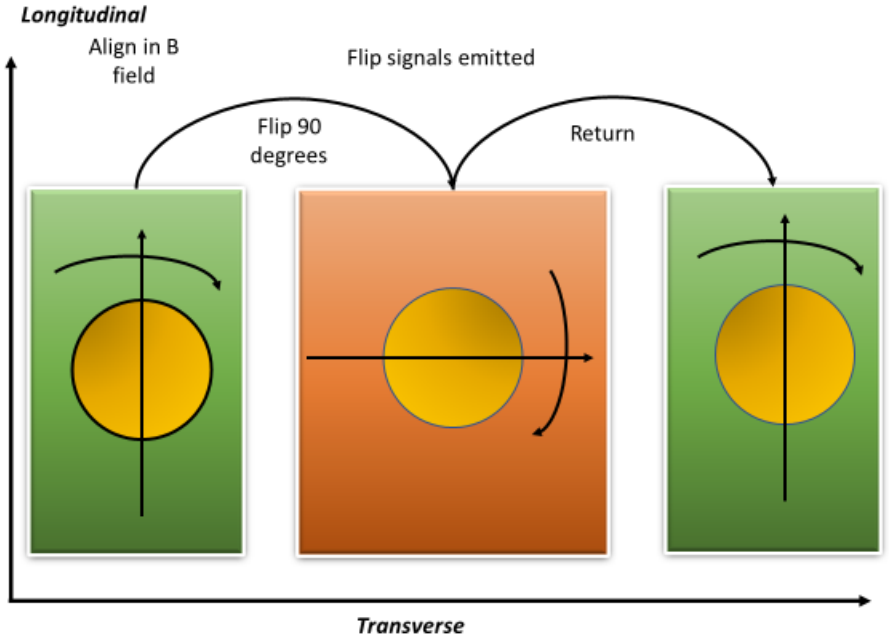
As we noted before, inverting by means of Fourier transforms, yields the spatial density, voxel by voxel.

6. MULTIPLE SCANS THEN MAP OUT THE COMPLETE 3 DIMENSIONAL SURFACE.

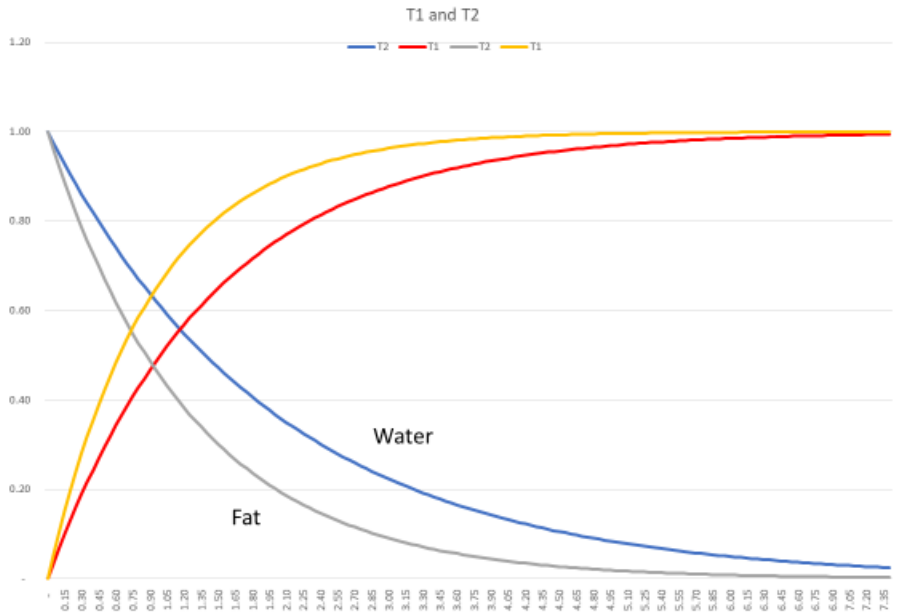
We then just do this slice by slice and get the final result.

This is the simple version. There are of course many subtleties which can further enhance what we see but understanding the basics is essential.

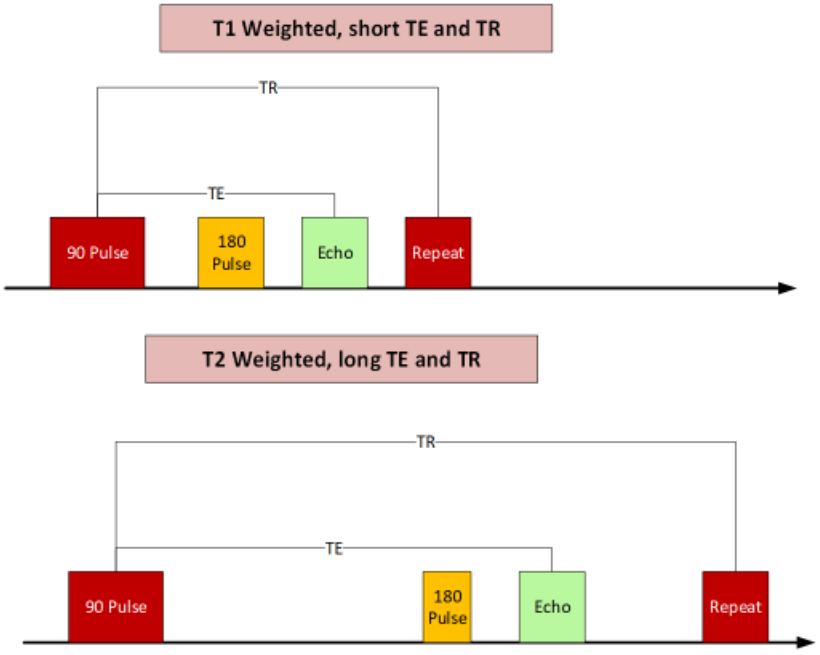
Let us briefly summarize via descriptives. Below we show the flipping scheme which yields echoes which we measure. First in a strong steady field, with gradients to be shown later, we have aligned hydrogen atoms all at frequencies dependent on the field at that point. Then we flip the field, and the flip it back. The atoms flip orientation, keep the frequency, but emit a signal, the echo.



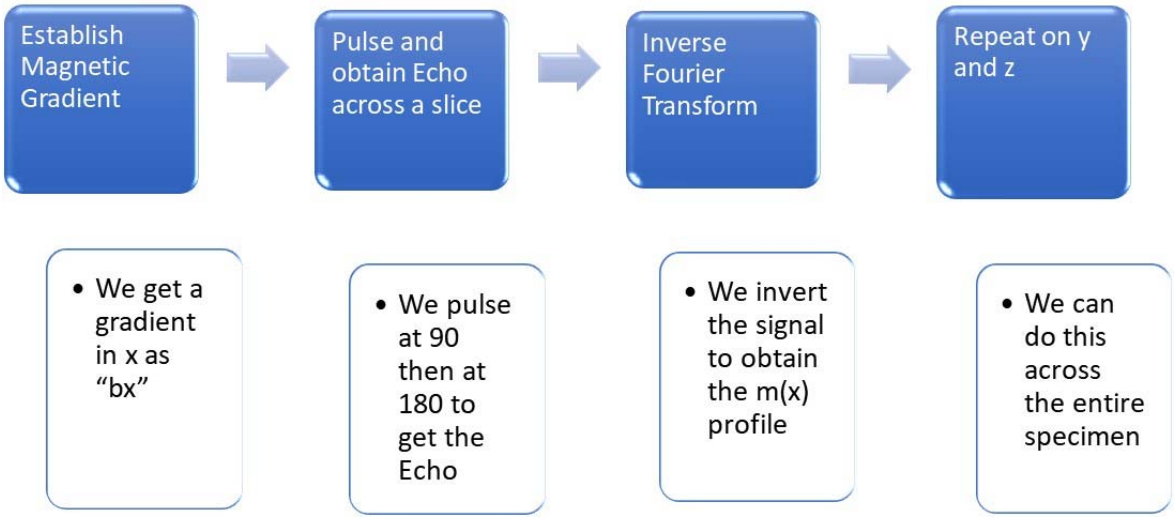
There are two directions, longitudinal or that in line with the original field and transverse or that in line with the flip. Now the signals also are reflective of these directions. T1 is the signal reflective of the signal going back to the original longitudinal and T2 the signal attaining and going from the transverse. We measure T2 echoes. The signals decay or saturate depending on what is happening and we show that below. In addition the time constants of T1 and T2 signals is dependent on what material is being sensed such as water or fat, bone or muscle.



Now there are two basic imaging schemes. We show them below. One is T1 weighted, T1WI, and here we use a short TE, or time to echo or the 90 degree flip, and short TR, the time to repeat the process. The second one is T2 weighted or T2WI where we have long TE and TR. Each of these schemes provides different contrasts. We often use T2WI.



Repeating the overall process we show it below:



Now there can be a multiplicity of signalling and gradient schemes. Each has a desirable result. However patient exposure time is often the limiting factor. A typical T2WI with contrast may take 45 minutes as compared to a 5 min CAT scan.

4.2.2 Current Progress

Multiparametric MRI (mpMRI) has come into its own. It has seen extensive use in PCa diagnosis and as noted by Gai and Haider:

Multiparametric-magnetic resonance imaging (mp-MRI) has shown promising results in diagnosis, localization, risk stratification and staging of clinically significant prostate cancer. It has also opened up opportunities for focal treatment of prostate cancer. Combinations of T2-weighted imaging, diffusion imaging, perfusion (dynamic contrast-enhanced imaging) and spectroscopic imaging have been used in mpMRI assessment of prostate cancer, but T2 morphologic assessment and functional assessment by diffusion imaging remains the mainstay for prostate cancer diagnosis on mp-MRI.

Because assessment on mp-MRI can be subjective, use of the newly developed standardized reporting Prostate Imaging and Reporting Archiving Data System scoring system and education of specialist radiologists are essential for accurate interpretation. This review focuses on the present status of mp-MRI in prostate cancer and its evolving role in the management of prostate cancer… T2-WI is the workhorse of prostate MRI. It provides high spatial resolution and defines the zonal anatomy differentiating the peripheral zone from the transition zone, the central zone, ejaculatory ducts, anterior fibromuscular stroma, seminal vesicles and the urethra. The neurovascular bundles are also outlined on T2WI. The peripheral zone has high signal intensity on T2WI, reflecting its higher water content, and cancer in the peripheral zone appears as an area of lower signal.

However, low T2 signal in the peripheral zone may also be seen in benign abnormalities, including prostatitis, fibrosis, scar tissue, postbiopsy hemorrhage or post-irradiation. The heterogenous appearance with multiple BPH (benign prostate hyperplasia or benign enlargement of the prostate) nodules makes assessment for cancer more difficult in the transition zone, especially for the lessexperienced reader.

Functional imaging is not always helpful in the assessment of transition zone tumor as areas of benign stromal or proliferating hyperplasia may show heterogenous enhancement on DCE and restricted diffusion on DWI. Morphological features on T2WI, such as an "erased charcoal" appearance, indistinct margins of the nodule, extension of low signal into peripheral zone, lenticular shape, extension to fibromuscular stroma and local invasion, help to differentiate tumor from benign tissue, but again some BPH nodules may also not be clearly demarcated or encapsulated and therefore this remains a well-identified limitation of mp-MRI. As such, T2WI is considered the dominant of all the mp-MRI sequences for detection of cancer in the transition zone.

4.2.3 DWI

The diffusion weighted MRI, DWI, uses certain properties of water and its diffusion in cells as a means to ascertain the benign or malignant state of certain sampled areas. As Turkbey et al have noted:

In 1965, Stejskal and Tanner proposed the application of a symmetric pair of additional gradients on either side of the 180˚ refocusing radiofrequency pulse. The Stejskal-Tanner sequence is still the basis of modern DWI.

For static water molecules, the phasing effect caused by the first gradient will be reversed by the second gradient, leading to no signal loss; however, this phasing effect will not be completely reversed if the water molecules are not stationary, which results in the observed well-known diffusion signal decay. The amount of diffusion weighting is determined by the b value, which describes the amplitude, duration of the applied gradient, and time interval between the two diffusion gradients. The degree of signal attenuation from water molecules is correlated with the b value. Low b values indicate flow or perfusion movement, whereas high b values (e.g., b=1.000 s/mm2) indicate slow-moving water molecules.

A minimum of two b values are necessary for DWI and the calculation of ADC. The evaluation of the data provided by DWI can be either qualitative or quantitative. Qualitative evaluation involves visually assessing the relative signal intensity attenuation of image obtained at different b values and enables tissue characterization based on differences in water diffusion. From a clinical point of view, qualitative assessment can help to detect and characterize tumors, monitor the treatment response, and detect recurrence in patients with cancer.

Trace or index diffusion-weighted images are the sum of images acquired by applying diffusion gradients in each of the three orthogonal directions. The signal intensity in these images is affected by both water diffusion and T2 relaxation time; thus, a tissue area with a very long T2 relaxation time may reveal a high signal that may be misinterpreted to represent restricted diffusion at DWI, a phenomenon that is also known as "T2 shine-through".

An additional entity is the "T2 dark-through" effect, which indicates hypointensity in both DWI and T2W MRI. Such effects, mainly secondary to susceptibility effects, are commonly seen in hematomas. The use of appropriate TE and b values may reduce these effects. In biological tissues, a quantitative analysis of DWI can be performed by calculating an ADC based on the relative signal intensity change of the tissue with increasing b values. ADC maps are based on the slope of the line depicting signal loss with rising b values. Values can be calculated on a voxel-by-voxel basis to provide ADC maps. Notably, restricted diffusion in highly cellular areas results in low ADC values compared with less cellular areas, which show higher ADC values.

4.2.4 DCE

Dynamic contrast enhanced MRI is a technique which employs contrast medium in a dynamic manner. Thus it is somewhat self-explanatory. As Padhani has noted:

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is performed after the administration of intravenous contrast medium to noninvasively access tumor vascular characteristics. DCE-MRI techniques utilizing low-molecular-weight contrast media have successfully made the transition from methodological development to preclinical and clinical validation and are now rapidly becoming mainstream clinical tools. DCE-MRI using macromolecular contrast medium (MMCM) can also assay microvascular characteristics of

human tumor xenografts. MMCM approval for human use will occur soon. The success of both techniques depends on their ability to demonstrate quantitative differences of contrast medium behavior in a variety of tissues. Evidence is mounting that kinetic parameters correlate with immunohistochemical surrogates of tumor angiogenesis, including microvessel density, and with pathologic tumor grade. DCE-MRI is being applied to monitor the clinical effectiveness of a variety of treatments, including antiangiogenic drugs. Kinetic parameter changes following treatment have correlated with histopathological outcome and patient survival

As Nguyen et al have recently noted:

Functional dynamic contrast-enhanced MRI (DCE-MRI) can assess the microcirculation and visualize the neoangiogenesis of malignant tissues via the dynamic signal enhancement of a *contrast agent. DCEMRI has already demonstrated good interobserver agreement and high accuracy in the differentiation of muscle-invasive from non-muscle-invasive bladder cancer. High field 3T MRI has been shown to be superior to lower field strength MRI in the spatial resolution, signal-to-noise ratio, contrast-to-noise ratio, and the delineation of the depth of tumor invasion in different types of cancer.*

To date, there has only been one study that used 3T MRI (with conventional T1-weighted and T2-weighted Imaging) for the local staging of bladder cancer. No prior study to assess the capability of 3T MRI with functional imaging for the localization of bladder cancer has been reported. We conducted a multi-parametric MRI study to systematically evaluate the capabilities of conventional and functional MRI for the localization, staging, and assessment of therapeutic response of bladder cancer.

Thus using T1, T2, DWI and DCE in some coordinated and integrated manner, correlative MRI imaging may present a strong alternative.

4.2.5 MRI Accuracy

Now the question is; how accurate is the use of MRI technologies. As Miraj et al have noted:

Accurate preoperative evaluation of proven bladder carcinoma is important because therapy depends on the clinical stage of the disease. There is a significant error rate (up to 50%) in the clinical staging of primary bladder tumors. Whilst accurate for superficial tumors (T1 and lower), the main error occurs in muscle invasive tumors (T2a and higher) with difficulty in assessing infiltration, lymphadenopathy and distant disease. MRI has been shown to be accurate in staging primary bladder cancer when compared to pathological specimens and this accuracy is not dependent on magnetic field strength. This prospective study was conducted with the aim of determining the accuracy of MRI in the staging of bladder carcinoma by correlating the MR diagnosis with that of the pathologic diagnosis.

The normal bladder wall is depicted as a thin (2 mm thick) linear low-intensity structure that is easily differentiated from urine, which displays higher intensity on T2-weighted images. [Contrast-enhanced MR and diffusion weighted MR (DW-MRI) can likely distinguish between non-muscle invasive bladder cancer and muscle invasive cancer with >80% accuracy. Invasion

of the deep muscle layer (Stage T2b) was considered present when the low-signal-intensity line was disrupted completely by high signal intensity in the region underlying the tumor in the absence of extension into the perivesical fat.

The cellular layers are always a struggle for any of imaging. How great a resolution can one achieve in what time period. They continue:

Such a finding was found on MR imaging in 7 (28%) of our patients. Deep muscle invasion was correctly assessed in 22 of 23 cases. In one case, it was underestimated as stage T2a. ***Underestimation by MRI in this case was a result of interpretational error possibly due to poor image quality. However, misinterpretation may also occur at this point due to a chemical shift artifact that usually occurs at the water- fat interface (between the bladder and perivesical fat) as a result of the difference in resonance frequency between fat and water protons****.*

The chemical shift artifact can be recognized as a dark band along the lateral wall on one side and a bright band along the lateral wall on the opposite side on transverse image.

In extreme cases, the chemical shift artifact may lead to apparent thickening of the bladder wall on one side and absence of the bladder wall on the contra lateral side. Knowledge of this artifact coupled with additional imaging along different planes helps avoid misinterpretation of this artifact as deep muscle invasion. Invasion of perivesical fat by tumor was considered to be present when a soft-tissue mass with signal intensity similar to that of primary tumor on both T1- and T2-weighted images extended into the perivesical fat. Invasion (Stage T3b or above) or absence of involvement (Stage T2b or below) of perivesical fat was correctly diagnosed in 15 of 18 cases. There were, however, 3 false negative cases that had microscopic invasion of perivesical fat which was missed on MR images.

Another accuracy view is contained in Mustafa et al have noted:

In this study, despite small differences between the results of the MRI and pathology, Dynamic MRI was found to be an accurate modality for assessment of tumor staging, and its routine use in bladder cancer staging can lead to significant improvement of diagnostic accuracy of the staging and treatment planning and hence improvement of the prognosis of the patients and their survival rates. Furthermore, the use of Dynamic MRI systems with higher magnetic field and imaging techniques standardized with higher resolution could further enhance the accuracy of the method. Further studies with larger sample size may also help to validate the results of this study. …

A point that was considered in the present study rather than previous studies was the correlation of tumor stage with slope of time intensity curves of tumor in dynamic changes. Tumor vessels are not normal and tumor epithelial cells within the inner surface of tumor develop gaps. The blood leaking out from the distance between endothelial cells, permeability, and neovascularity of tumor increase abnormally and tumors with higher angiogenesis have higher risk of local recurrence.

By Dynamic MRI, the peak of the curve occurs in areas with uptake of contrast, which represents increased permeability, abnormal vascularity, and higher malignancy of tumor.

The positive correlation and significant relationship between tumor stage and signal enhancement slope of tumor time-intensity curves suggest that the peak time-intensity curves occur with great slope as tumor stage increases. The relationship can be helpful in diagnosis of severity and progression of tumors, as the slope of the curves is steeper in the non-organ-confined tumors.

Finally in a study by Bouchelouche et al they have stated:

Optical cystoscopy of the bladder is a time honored diagnostic method that provides high resolution scanning of the bladder mucosa. ***MR Cystoscopy (MRC)*** *can be a useful adjunct to conventional cystoscopy to localize difficult-to-see lesions for instance, those that require retroflexing of the scope.*

There are two basic methods for performing MRC:

1-Acquiring 3D T1W MRI after opacification of the lumen with gadolinium administered either retrograde by catheter or intravenously,

2-Acquiring 3D T2W MRI after luminal distention with urine without any specific preparation.

The 3D data sets obtained from both methods can be evaluated by multi-planar, 3D or virtual cystoscopic "fly-through" reconstruction methods. There are a limited number of publications about the utility of MRC for BCa detection and staging. Lammle et al. reported detection rates of 90.9% and 100% for all tumors and for tumors greater than 1cm, respectively in 24 BCa patients.

Beer et al. reported sensitivity and specificity of 91% for MRC in 32 patients with 43 lesions. MRC has several advantages over conventional cystoscopy such as being relatively impervious to hematuria, urethral strictures and anterior bladder wall lesions (which can be difficult to reach via cystoscopy), however, its limitations include a time consuming costly procedure requiring expertise which has difficulty detecting of flat lesions. Importantly, it is not possible to perform a biopsy with MRC

The issue of time and cost is a critical factor. MRIs take considerably longer to effect and their costs can often be prohibitive, especially if reimbursements are denied or low.

One final point is MRI resolution. Recall that the thickness of the urothelial layer is a maximum of 210 microns. That is seven cells stacked atop of one another. The resolution equation for MRI scanning is[27]:

[27] See Westbrook and Talbot, p 139

$$S(m) = \frac{TBW(KHz)}{\gamma(MHz/T)G(mT/m)}$$

Thus the smaller the slice the smaller the bandwidth and the larger the gradient. The smaller the BW the longer the scan and the larger the gradient the bigger the magnet. Thus a 3T magnet allows for better gradient. It is not at all clear, however, that we can achieve the 210 micron or better in a timely manner.

We can use a simple example. Consider H and 1.5T magnet. We know:

$$\gamma = \frac{\omega}{B} = \frac{64MHz}{1.5T} = 40(MHz/T)$$

Thus if we use say a 1 KHz BW and a slice of 100 (mT/M) we obtain:

$$S(m) = \frac{1KHz}{40(MHz/T)100(mT/m)}$$

$$= \frac{1}{4000}(m) = 250\mu$$

Thus this is in the range of the epithelial layer.

4.3 PET

PET imaging is a form of nuclear medicine imaging using active tracer molecules which enable the emission of such particles as gamma rays from positrons. The system focuses on such metabolic activity that may be useful in ascertaining the presence of a malignancy. PET systems have a more gross detection capability and lack the detailed localization capability of MRI.

As Schoder and Larson had noted:

Prostate cancer, renal cancer, bladder, and other urothelial malignancies make up the common tumors of the male genitourinary tract. For prostate cancer, common clinical scenarios include managing the patient presenting with 1) low-risk primary cancer; 2) high-risk primary cancer; 3) prostate-specific antigen (PSA) recurrence after apparently successful primary therapy; 4) progressive metastatic disease in the noncastrate state; and 5) progressive metastatic disease in the castrate state. These clinical states dictate the appropriate choice of diagnostic imaging modalities.

The role of positron emission tomography (PET) is still evolving but is likely to be most important in determining early spread of disease in patients with aggressive tumors and for monitoring response to therapy in more advanced patients. Available PET tracers for assessment of prostate cancer include FDG, 11C or 18F choline and acetate, 11C methionine, 18F fluoride, and fluorodihydrotestosterone. Proper staging of prostate cancer is particularly important in

high-risk primary disease before embarking on radical prostatectomy or radiation therapy. PET with 11C choline or acetate, but not with FDG, appears promising for the assessment of nodal metastases.

PSA relapse frequently is the first sign of recurrent or metastatic disease after radical prostatectomy or radiation therapy. PET with FDG can identify local recurrence and distant metastases, and the probability for a positive test increases with PSA. However, essentially all studies have shown that the sensitivity for recurrent disease detection is higher with either acetate or choline as compared with FDG. Although more data need to be gathered, it is likely that these two agents will become the PET tracers of choice for staging prostate cancer once metastatic disease is strongly suspected or documented.

18F fluoride may provide a more sensitive bone scan and will probably be most valuable when PSA is greater than 20 ng/mL in patients with high suspicion or documented osseous metastases. Several studies suggest that FDG uptake in metastatic prostate cancer lesions reflects the biologic activity of the disease. Accordingly, FDG can be used to monitor the response to chemotherapy and hormonal therapy. Androgen receptor imaging agents like fluorodihydrotestosterone are being explored to predict the biology of treatment response for progressive tumor in late stage disease in castrated patients.

The assessment of renal masses and primary staging of renal cell carcinoma are the domain of helical CT. PET with FDG may be helpful in the evaluation of "equivocal findings" on conventional studies, including bone scan, and also in the differentiation between recurrence and posttreatment changes. The value of other PET tracers in renal cell carcinoma is under investigation. Few studies have addressed the role of PET in bladder cancer.

Because of its renal excretion, FDG is not a useful tracer for the detection of primary bladder tumors. The few studies that investigated its role in the detection of lymph node metastases at the time of primary staging were largely disappointing. Bladder cancer imaging with 11C choline, 11C methionine, or 11C- acetate deserves further study.

4.4 NUCLEAR MEDICINE

In contrast to PET and its related technique SPECT, general nuclear medicine is more focused on organ by organ and the scans generally look at high concentration of the nuclear tracer such as in bone metastasis in PCa.

As Jana and Blaufox have noted:

In the United States, bladder cancer is the fourth most common malignancy in men.197 Most of the newly diagnosed bladder cancers are low grade and noninvasive. There is a high grade cancer also, which is characterized by rapid progression with local invasion, extension to the adjacent organs, and development of regional and distant metastases. The invasive disease confined to the pelvis is treated with radical cystectomy and pelvic lymphadenectomy.

The cure rate of organ-confined bladder cancer is more than 70%. On the other hand the presence of lymph node metastases increases the chance of recurrence and distant disease, and this group has a 5-year survival of only 20 to 25%.198-201 Preoperative diagnosis of local extension would help to select appropriate bladder-sparing surgery, nerve- or vaginal-sparing operations, or pelvic exenteration.

Historically, the staging of bladder cancer with various imaging modalities has been limited.

CT scanning can detect only gross tumor extension beyond the bladder wall with an accuracy of 64 to 92%.202 The accuracy of CT in detecting lymph node metastases ranges from 70 to 90% with false-negative rates as high as 40%.203 Similarly, MRI has been disappointing with regard to staging, with accuracies ranging from 60 to 75%.204 The major limitation of these imaging modalities is the dependence on nodal size and anatomical changes to make a diagnosis of cancer. Given the ability of PET to detect differential metabolic activity, investigators have begun exploring the use of PET to stage bladder cancer.

The role of FDG-PET in the detection of localized bladder cancer is limited because of the difficulty in differentiating radiotracer activity excreted into the urine from tumor activity in the bladder or adjacent lymph nodes. However, FDG-PET has demonstrated some utility in identifying distant lymph node involvement and distant disease.

Kosuda and coworkers205 reported that PET imaging identified 17 of 17 patients with metastatic disease (lung, bone, and remote lymph nodes) as well as 2 of 3 patients (67%) with localized lymph node involvement. Similarly, Heicappell and coworkers reported a 67% detection rate for local nodal disease. Investigators have attempted to improve the sensitivity of PET by using tracers that are not excreted in the urine. Ahlstrom and coworkers206 found 11C-methionine is superior to FDG, however, tumor was identified with a sensitivity of 78% (18/23) only with methionine PET. They also reported that tracer uptake was proportional to tumor stage.

4.5 ULTRASOUND

Ultrasound has significant usefulness as a strong adjunct. It can be used as an initial investigative tool and then used in correlative imaging.

As Tadin et al have noted:

Urinary bladder cancer (UBC) is dominantly the cancer of the elderly occurring primarily in the 6th, 7th and 8th decade of life. The aim of this study was to evaluate diagnostic accuracy of ultrasound T-staging (UTS) of UBC in the group of elderly patients. In 152 elderly patients referred to transabdominal ultrasound examination in two different facilities (76 each) due to various symptoms (primarily painless gross or microscopic haematuria) UBC was diagnosed. Initial UTS at the moment of detection was performed and compared with final histological T-staging (HTS). A high level of conformity between UTS and HTS was detected.

In a total of 152 patients with UBC there were 115 (75.66%) patients with complete match between the UTS and HTS, 24 (15.79%) patients with minimal variation within one stage, and 13 (8.55%) patients with one stage difference between the UTS and HTS. The best result was established for the stage T1, where the accuracy was 94.5%. In other stages the accuracy was between 84.9% and 91.8%. The Youden's index for all the stages was over 0.6. UTS has a high diagnostic accuracy, especially for stages T1 and T2.

It is extremely useful tool in differentiating the superficial UBC from the muscle-invasive one, being of significant importance in planning the further treatment of elderly patients and having important role in choosing appropriate surgical approach …

Diagnostic accuracy of UTS is high for stages T1 and T2, slightly lower for stages T3 and T4, and insufficient in differentiation between stages T3a and T3b. Therefore, it is extremely useful in initial assessment of newly detected UBC with respect to differing superficial tumour from the muscle-invasive one which is essential for planning the further treatment14. Furthermore, it is highly useful noninvasive tool for assessing the penetration of UBC into surrounding structures.

5 OBSERVATIONS

We now have several observations regarding the question at hand. Let us begin by again phrasing the issue:

CAN IMAGING MODALITIES, ESPECIALLY MPMRI, BE USED AS AN ADJUNCT IN STAGING BLADDER CANCER? FURTHERMORE, CAN MPMRI BE USED IN PLACE OF INVASIVE PATHOLOGICAL STUDIES IN DIAGNOSING, STAGING AND PROGNOSTIC EVALUATION OF BLADDER CANCER?

Clearly cystoscopic examination is the current gold standard. First it collects tissue samples and second, it permits the immediate resection of suspected lesions. However, it is invasive and it may not provide full diagnostic results. It also may miss portions of the bladder where there may be obscured lesions. Furthermore, once a cystoscopic removal is performed there is residual scar tissue which may later be observed as a suspicious area on MRI examinations.

We have seen increased acceptance of mpMRI in PCa and it is used in conjunction with ultrasound in prostate biopsies. However as we have noted previously use of mpMRI also detects the scar tissues and fibrosis from past biopsies. There does not appear to be significant studies indicating how these scar tissues can be compared and eliminated on subsequent MRI examinations at this time.

5.1 COMPARISONS

We first make a comparison of the various techniques we discussed herein.

Class	*Method*	*Advantages*	*Disadvantages*
Cystoscopy			
	White Light	All cystoscopies have the advantage of visualization as well as tissue sampling.	Invasive and may miss tissues.
	Computer Assisted		
	Narrow Band		
	Confocal		
	Optical Coherence	This technique is used extensively in other areas and allows for tissue depth examination without excision.	Lack the disadvantage of depth loss.
Ultrasound			
	Two dimensional		
	Contrast Enhanced		
CT			
	Computed Tomographic Urography		
	CT		
MRI			
	T1W	T1 has limited use	T1 weighting is less sensitive due to water and fat overlap
	T2W	This is the standard approach and is well understood	Has less sensitivity to specific lesions
	DWI	Allows for the determination of malignant areas due to water diffusion	Has sensitivity to bladder filling. Can be stressful on patients.
	Dynamic Contrast	The dynamic contrast allows for seeing changes as tissues are perfused giving arguably better specificity.	May require longer scan times.
	Lymphotropic Nano MRI		
	mpMRI	This is a fully integrated system of multiple MRI modalities optimized for specific tissues	
PET			

Class	*Method*	*Advantages*	*Disadvantages*
	FDG PET/CT	PET tend to focus on metabolically active regions enhancing active malignancies	Lacks localization capability.
	C-Choline PET/CT	Same as above	
	F-NaF PET/CT	Same as above	

5.2 CORRELATIVE AND INTEGRATED DECISION METHODS ARE NECESSARY

One of the more recent capabilities is the integration and correlation of disparate imaging modalities. Thus do we correlate T2WI, DCE, DWI images, and if so with what? We discuss this later.

5.3 STANDARDIZATION

As RECIST has become a standard (see Eisenhauer et al) for certain solid tumor trials one will need the development of a putative standard in some complex integrated metric.

Rizzo et al discuss the complexity of radiomics imaging by noting:

The radiomic process can be divided into distinct steps with definable inputs and outputs, such as image acquisition and reconstruction, image segmentation, features extraction and qualification, analysis, and model building. Each step needs careful evaluation for the construction of robust and reliable models to be transferred into clinical practice for the purposes of prognosis, non-invasive disease tracking, and evaluation of disease response to treatment.

After the definition of texture parameters (shape features; first-, second-, and higher order features), we briefly discuss the origin of the term radiomics and the methods for selecting the parameters useful for a radiomic approach, including cluster analysis, principal component analysis, random forest, neural network, linear/logistic regression, and other. Reproducibility and clinical value of parameters should be firstly tested with internal cross-validation and then validated on independent external cohorts. This article summarises the major issues regarding this multi-step process, focussing in particular on challenges of the extraction of radiomic features from data sets provided by computed tomography, positron emission tomography, and magnetic resonance imaging

Now Panebianco et al have performed analyses on BCa using mpMRI and in so doing have suggested a scoring system. This was done for T2WI, DCE and DWI scans. It is not clear that this system would attain general acceptance and in addition it lacks morphological characteristics.

5.4 CLINICAL VALIDATION

Clinically validating the proposition is a complex inter-disciplinary and inter-organizational effort. It is posing a new method for diagnosis and arguably the abandonment of a standard. The complexity can be quite significant.

5.5 CROSS DISCIPLINE COORDINATION

In many ways the changing of a diagnostic procedure that crosses multiple disciplines can be at the least problematic. Currently urologists, surgeons, perform the examination as well as follow on treatment. Pathologists interpret the results from any tissue sampling and opine upon the state and staging of the lesions. Only as a secondary player do the radiologists enter the process.

If one can answer the fundamental question strongly in the affirmative could one expect the commencement of a cross discipline change. Moreover it would be essential to get CMS to approve the procedure for billing purposes. That in itself could be time consuming as we have seen in PCa.

5.6 CANCER: WHEN IS IT REALLY CANCER?

We have discussed this issue previously at length. CIS, carcinoma in situ, is generally a collection of cells whose behavior is aberrant yet are still generally localized. This is not a dispositive definition but is descriptive. Many pathologists depending on the location of the lesion may or may not invoke the CIS name. Some avoid carcinoma in toto and others will call it carcinoma notwithstanding. Thus when do we call a lesion a cancer and does CIS have any place going forward?

5.7 THE GENETICS OF SINGLE CELLS

The old paradigm of cancer being evoked from a single aberrant cell and then expanding ever more is being called into question. Single cell genetic analysis will be the gold standard going forward but such a standard presents a massive data analysis and presentation problem. We see genetic cell profiles collected by many. In addition we see the liquid biopsy approaches tested for a variety of blood and urine borne markers. Yet the challenge will be single cell genetic tests.

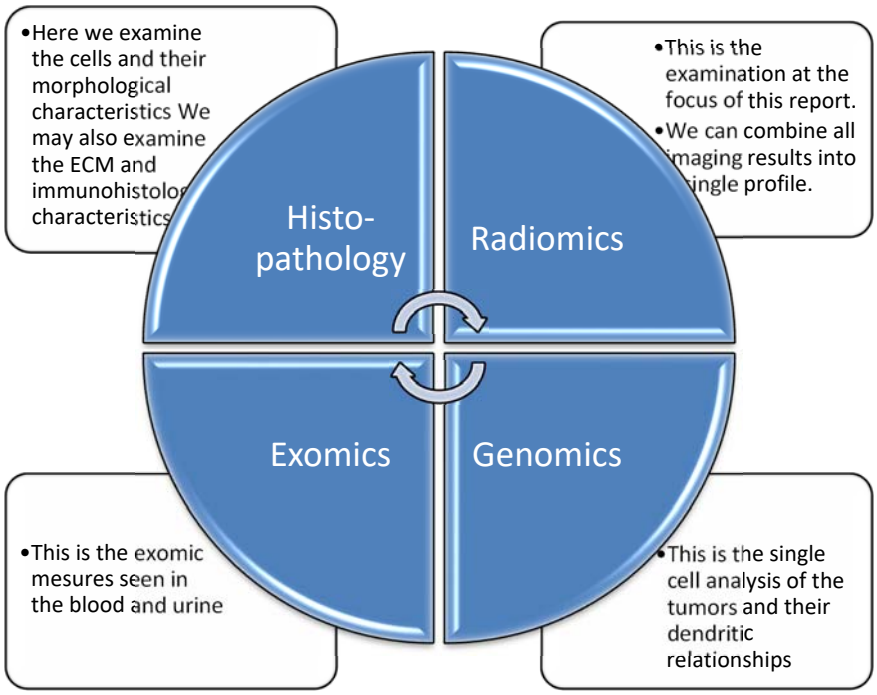
Consider if you will the case of a biopsy and we examine say 1,000 of the 20,000 or more cells. We can utilize one of several single cell extraction system, then taking the cell sequence it as may be required. Then compare the sequences, along with morphological presentations to assess the makeup of the lesion. This is a highly complex data problem. For example, can we ascertain a stem cell, can we ascertain progeny of the cells? Can we create a dendrogram linking the cell matrix?

5.8 TUMOR MICRO ENVIRONMENT

The tumor microenvironment, TME, is as critical as the cells of the tumor itself[28]. All too often they are neglected. Tumor associated macrophages for example are often a critical marker for an aggressive lesion despite the fact that the cells may appear less aggressive. Thus, any attempt to perform a diagnostic study, must in our opinion, envision some presentation of the TME.

5.9 THE HOLISTIC APPROACH

Finally, how do we add all these elements into a totality. We depict the issue below:



5.10 IS THERE A ROLE FOR AI?

This is one of the oft noted issues in medicine. First let me state that having spent over fifty years in and amongst the various evolutions of what is called AI that AI qua an all-encompassing capability does not exist. There are tools and techniques which can be used in common but no single AI "thing" can be taken and used. In fact each time we seek an AI approach we create a new silo of expertise optimized for that specific application. Thus speech recognition is now a deep silo of ever expanding intricacy, albeit using some of the general tools for classification,

28 https://www.researchgate.net/publication/336116071_Tumor_Associated_Immune_Cells_On_the_one_hand_and_on_the_other_hand and https://www.researchgate.net/publication/315374581_Extracellular_Matrix_vs_Intracellular_Pathways

identification, and segmentation. Image identification has progressed such as in identifying blood smears and to a limited degree in radiology. Yet AI techniques seem often so easy to fool[29].

The biggest problem I see in AI is the neural network approach. Science[30] has an article commenting on the complexity of using AI techniques to determine a simple lung infection amongst patients. The article notes:

When the algorithm was tested on a different batch of Mount Sinai x-rays it performed admirably, accurately detecting pneumonia 93% of the time. But .... also tested it on tens of thousands of patient images from two other sites: the National Institutes of Health Clinical Center in Bethesda and the Indiana Network for Patient Care. With x-rays from those locations—where pneumonia rates just squeaked past 1%—the success rate fell, ranging from 73% to 80%, the team reported last year in PLOS Medicine. "It didn't work as well because the patients at the other hospitals were different," ... says. At Mount Sinai, many of the infected patients were too sick to get out of bed, and so doctors used a portable chest x-ray machine. Portable x-ray images look very different from those created when a patient is standing up. Because of what it learned from Mount Sinai's x-rays, the algorithm began to associate a portable x-ray with illness. It also anticipated a high rate of pneumonia, boosting misdiagnoses.

This is not that unexpected. The AI technique, most likely a neural network, uses many data point but no knowledge. It is akin to my argument that if Newton had used AI to determine gravity it may very well have included some metric including the color of the Kings undergarments! The lesson to be learned is that any AI neural network must be trained on the right parameters not just everything and AI has not yet reached to stage where it can independently determine those parameters.

I have been considering the whole issue of AI. You see I have been looking at this for about fifty plus years now. In fact, when I arrived at Warner in 1980 or so, my boss, Gus Hauser, sent me a note, I believe the third day I was there, to ask to report to him on AI. I knew Patrick Winston at MIT, he had published a book on AI from his perspective, but I also know Minsky, Papert and others, so I had been at the AI watering hole[31]. To me AI was just the name of a watering hole, not a thing unto itself. My opinion then was it was still a work in progress, very little progress. Skip ahead to 1986 and as the new Executive Director of Research at NYNEX, now Verizon, I was being pressured to develop a whole area in Neural Networks. I knew this area well, but I was also assured that the then current computer systems were inadequate. Namely in order to do a lot of the neural network approaches one needed massive computer capacity, which then was lacking.

Even earlier, in 1971 I had a brief sabbatical at Bell Labs trying to track Soviet subs. Massive data focused on pattern recognition. I tried all of the largest scale data and deep learning

[29] https://www.nature.com/articles/d41586-019-03013-5

[30] https://science.sciencemag.org/content/364/6446/1119

[31] See the works by the authors as attached.

algorithms that were available on the then most advanced IBM 360 computers. They did not work well. Fundamental problems existed in gathering the data but that fact that there were systemic flaws in the detection logic did not skink in and wheels just kept spinning in hopes of better pattern recognition, a branch so to speak of the nascent AI.

Now back in the mid-60s I spent time at the MIT Instrumentation Lab, working on guidance and navigation systems for Apollo and other projects. That is when I became enamored by the three-body problem. The force on three bodies and the resultant sets of equation can be determined as follows:

$$F_1 = m_1 \frac{d^2 x_1}{dt^2} = k \frac{m_1 m_2}{|x_1 - x_2|^2} + k \frac{m_1 m_3}{|x_1 - x_3|^2}$$

and likewise, for the other two accelerations. From the solutions of these three calculations we can determine the dynamics of a spacecraft going between the earth and the moon. Now these equations are a result of two of Newton's laws of gravity; (i) force mass and acceleration, and (ii) force, mass and distance.

Now let us consider how Newton may have approached this problem using massive amounts of data and neural networks. Namely let us assume Newton could not think but he was a great coder. So Newton sees this apple fall from the tree and he thinks that there may be something here he could use to predict lots of other things, such as the trajectory of a cannon used in battle. So Newton goes out and collects tons of data.

For example, since he has no underlying theory he must just collect whatever he can. He is interested in such things as inputs and outputs of this neural network so he must a priori define these elements. This is the first step. But, and this is critical, he can only measure what he can define and what he can measure with the tools available to him.

So Newton sits under the apple tree and gets hit on the head with a falling apple. He then wants to know why the apple fell and how fast it was going when it hits his head. What results would Newton like to get as the output of his neural network? They may be:

1. Speed of the apple when it hits his head
2. Time it takes to fall
3. Distance it fell from the branch

We of course must assume he has the tools to measure these things. But he does measure them and most likely with errors. Also what inputs would Newton want to consider in his neural network as drivers of his outputs for which his neural network will determine from tons of data? They may be:

Temperature
Day of the week
Time of day

Color of his shoes
Species of tree
Amount of sunlight
Height of branch
Species of apple
Diameter of apple.
Weight of apple
Volume of the apple
Location of tree
Age of the tree
Latitude
Longitude
Angle of the sun
Color of the dress the Queen wore that day

and of course the list goes on. You see he has no idea what is driving his result so he just gathers tons of stuff he can measure just in case. Lacking a model he fills his network with "stuff".

So now Newton goes out and spends days and weeks under apple trees, he recruits many others, under order of the King, to also sit under apple trees, and after a while half of England is sitting under apple trees measuring the stuff Newton wants to get. Tons of data, massive amounts of data arrive.

Alas Newton can enter this into his neural network and let it grind away. So what is the result? Does he get the equation? No, not at all, he now has a big machine that requires you to enter tons of data to determine the speed of the apple when it hist your head under a specific tree, falling from a specific height. Is there some equation? Nope! Just the machine. Did we solve the three-body problem, not even close?

Now back to the three-body problem. In my Apollo days we had a computer with 64K memory, yes computer geeks, 64K, not Meg, not Gig, not Tera, K. That meant we had to think "smart" and not "hard". We needed to viscerally understand that three body problem, when and where and how much to fire the rockets for return.

Now let us move this to health care, say cancer diagnosis, prognosis and treatment. We now move to the current date where we are trying to diagnose say a thyroid tumor. They come in several varieties, papillary, follicular, medullary, and others. Now each of those have some sub classes. Our output is three stages; diagnosis (what type), prognosis (knowing what type what is an outcome), and treatment (knowing the first two what should we do). Thus one can consider a three output system, and some of the outputs having a multiplicity of subtypes.

The input is now what we can measure, what we have tools to measure. That is an important fact to remember since as we progress in knowledge and in tools what we can measure today may be a small amount of what can be done in a decade. There is no underlying physical laws to enforce, just tons of data and hopefully an answer.

Now consider an alternative approach. Suppose as, first with Newton, we had his laws. Then all we need is to find k, and solve the complicated set of equations. That value could readily be found by a somewhat dumb neural net. That is called a system identifies. Been there done that. But we could use a well know system presentation of cancers, one where we identify a measure, call it n(x,t), where n is an Nx1 vector where each element is the local concentration of a cell of a specific genetic composition, say a melanocyte with BRAF V600, or RAS, or N-cadherin and all possibilities thereof. In fact here we have possibly hundreds of genetic profiles, starting with the most benign and to the most malignant. n(x,t) may be a 1000x1 vector, and it is a function of time and space.

Now we ask how does this state, genetic state if you will, change in time, and on average. Well we have demonstrated the following. The rate of change is equal to a diffusion state, a flow state, and a growth state. This is a fundamental law of any organic system. This is Newton's law for cells.

Propagation Model: This equation provides a spatio-temporal model for the calculation of the number of specific cancer cells which are propagated by means of: (i) diffusion, (ii) flow, and (iii) proliferation.

$$\frac{\partial n(x,t)}{\partial t} = a\frac{\partial^2 n(x,t)}{\partial x^2} + b\frac{\partial n(x,t)}{\partial x} + cn(x,t)$$

Average Model: This model considers the calculation of the average number of malignant cells in a spatio-temporal manner when the cells mutate into N possible genetic variants. It calculates the average number by variant and thus is a vector equation containing the N variants.

$$\frac{\partial \overline{n(x,t)}}{\partial t} = \overline{Ln(x,t)} + \overline{\Lambda n(x,t)}$$

Now if we were to collect massive amounts of data we could determine a, b, c as above and then it could lead us to diagnosis, prognosis and treatment. It becomes a system identification and in turn optimal control problem, namely identifying the offending gene progressions and identifying where and when to stop that process.

Thus AI should be more than blind data churning. For it may have led Newton to a law dominated by the color of the Queen's hats and not a function of the product of masses. AI, to properly work, must have a set of underlying verifiable paradigms, models, which need further specificity. It should not just be a black box which tells us nothing about reality.

In the book by Gerrish, How Smart Machines Think32[1], the author purports to address the field of Artificial Intelligence by example, namely via the construct of machines that think. The examples he uses are chess playing, movie selection, the TV game of Jeopardy playing, playing Atari games or GO, and self-driving vehicles as examples. Now this does cover the field we

32[1] https://www.amazon.com/gp/product/0262038404/ref=oh_aui_detailpage_o09_s00?ie=UTF8&psc=1

generally call AI but it does present a powerful set of examples that demonstrate what AI may encompass.

The problem is that we can mostly agree as to what a machine is, simply hardware and software, plus some set of past and ongoing data regarding the target at hand but we have always had a difficulty of a clear definition of what thinking entails. We have had philosophers for centuries opining on this topic and thus despite a massive amount of new information of the neural process in the human we have the conundrum of definitions regarding a machine. At the best we have Turing and his putative definitions, which may be still quite wanting.

Instead of bemoaning the clarity in defining the process of thinking, and equally as well its correlative the term intelligence, we will focus a bit on the area of artificial intelligence as an artifact of computer science. All too often AI is in the eye of the beholder. Set loose upon the Press, it has almost taken a life of its own. Moreover, recently with the MIT push to create its first "college" as an entity almost sanctified by the AI mantra, it means whatever one seems to want it to mean. To that end we shall attempt to explore it a bit.

To start out, my view is shaped by half a century working on the periphery of AI. My personal experience is using what AI has as its fundamental techniques and applying them to a variety of situations. But before examining them let me step back a step. I would contend that much of what we are looking at today started with Wiener and his work on Cybernetics. It included McCullough, Pitts, Minsky, Papert, and even Chomsky to a degree. These were the idea folks, lacking the power of machines and with primitive algorithms. In many ways they were trying to emulate what they conceived of as the brain and its functions. I personally see a key initial played as Wiener, because he added the major element of uncertainty. One could see his gun tracking system as an integrated "thinking machine" and a world of uncertainty. Wiener's world was an analog world, which is how he envisioned things but also limited by the tools at hand. We have abandoned that world a bit but as we will see it may still be floating around in current thought.

Now to commence, there are two issues worth focusing on when examining AI. First, what types of embodiments would we generally accept as fitting the field of AI. Second, how is the field of AI practiced; namely are there a set of fundamental precepts and canonical tools or is it just a set of ad hoc problem solving. Thus, is AI akin to say 19th century medicine. A collection of techniques that may or may not work depending on the patient and the disease. 21st century medicine has become focused on causes and therapeutics that address the underlying causes. It is an extension of Koch's laws to genetic structures.

Let us consider several of the areas of "AI" focus and development. This is not a comprehensive list but merely descriptive. Minsky's landscape of AI, his book Society or Mind, is a somewhat rambling but highly insightful discussion of the dimensions. It has stood the test of time and is always worth a review.

1. Pattern Recognition

In a sense this is one of the oldest forms. It takes say a letter, A, and reads it and then using the output of the sensors determines the weighting that best gives A in the presence of 25 other letters. The list of letters is fixed as is their size and font type. The sensors are two dimensional and of a density that satisfies a reasonable text identification probability.

We can assume NXN or N2 sensors and the output of the sensors can be simply 0 or 1. We can then, assuming 26 letters, choose N2 weights so that by adding up the weighted N2 samples we can divide the output space into 26 regions each uniquely assigned to a specific letter. This is a simple pattern recognition algorithm. We optimize this by repetitively "teaching" the system by submitting the 26 letters again and again to maximize the detection rate and minimize the false alarm rate. We assume that some form of convergence exists.

Now there are many algorithms which have been developed for this class of problems. We can examine a finite set of precisely defined "letters" or objects and then begin to expand it to

We can even extend it to blood cell identification, and the whole field of pathology. Winston in the 1960s applied some of these techniques to blood analysis. The techniques have been also applied to EKG analyses. These however are significantly more complex. One can approach the EKG world from two dimensions. One is from the training perspective, where thousands of EKGs are presented and classified. Then the system uses this based to select a diagnosis. The second approach is the physical analysis approach. He we would assume to know the physio-electro dynamics of the heart. Then we would try to use the underlying model of reality to ascertain what was defective and attempt to match that with what we have observed thus identifying the underly defects from what has to change to match the results. It should be noted that the preceding two methodologies are also descriptors of the two sets of our attempts to describe how one gets to know things. Perhaps humans who are proficient in this area utilize both approaches.

The characteristics of this class of recognition system are:

1. Finite number of distinguishable classes of objects, albeit large classes.
2. Objects which have a finite set of identifiers, albeit large sets, such as shape, color, etc.
3. Objects which are static during recognition
4. Finite sets, albeit large sets, of objects

2. Speech Recognition

Speech recognition has reached a reasonable level of usefulness. Speech recognition is an example of a trained technique to detect answers to question and ultimately the actual collection of fully forms speech. It has evolved extensively over the past three decades and many techniques are available. One may question whether this is AI or just a technology. The question may be; is the system making decisions of any type or just matching utterances with written words.

One could perhaps combine this with an quasi AI system which emulates an interview with a psychiatrist, a physician, a professor, and then from the results of the interaction makes certain decisions. Yet these elements transcend the tasks of speech recognition.

3. Text Translation

Text translation is a complex process. Transliteration generally leads to nonsense text. One language has a structure and nuance which be absent from another. Even dialects can be strikingly different. My Sicilian Italian learned in my childhood was incomprehensible in Florence and insulting in Milan. My translations of Dumas can be childlike whereas a good translator can convey the drama of the author. Then again translating Pushkin can be even more challenging. Finally one should try translating legal documents from Arabic to English. Culture, religion, different language structures all lead to cumbersome results.

To quote from Joseph Stalin, not one know for either academic excellence or a broad understanding of cultures:

Thus, a nation is not a casual or ephemeral conglomeration, but a stable community of people. But not every stable community constitutes a nation. Austria and Russia are also stable communities, but nobody calls them nations. What distinguishes a national community from a state community? The fact, among others, that a national community is inconceivable without a common language, while a state need not have a common language. The Czech nation in Austria and the Polish in Russia would be impossible if each did not have a common language, whereas the integrity of Russia and Austria is not affected by the fact that there are a number of different languages within their borders. We are referring, of course, to the spoken languages of the people and not to the official governmental languages.

Thus, a common language is one of the characteristic features of a nation. This, of course, does not mean that different nations always and everywhere speak different languages, or that all who speak one language necessarily constitute one nation. A common language for every nation, but not necessarily different languages for different nations! There is no nation which at one and the same time speaks several languages, but this does not mean that there cannot be two nations speaking the same language! Englishmen and Americans speak one language, but they do not constitute one nation. The same is true of the Norwegians and the Danes, the English and the Irish. But why, for instance, do the English and the Americans not constitute one nation in spite of their common language?

This quote is descriptive of the sensitivity of language. Yes, the English and American speak a similar and mutually understandable language. But there are fundamental differences and thus any language translation must take these into consideration. Thus far it does not appear that any AI system accomplishes this.

4. Text Interpretation

"What do you mean by that?" may be a frequent question. We understand what was said, we can translate it but we may still have a lacking of meaning.

5. Information Retrieval (Q and A)

The game of Jeopardy is a classic example of information retrieval, via a question and answer scenario. Specifically we deal with the Question as well as the answer. As described by Gerrish, the IBM approach was complex, because it first required the parsing of the question and seeing what was asked for. Typically in the game there are categories of questions and then in each category a set of questions seeking the identity of some person, place or thing for which the specific question is the answer. This is a bit the opposite of our usual way of processing since here we see the answer posed and then seek to pose the question. However the same may apply in reverse. In either case it is still merely a case of checking known facts. It is static and certain and the answer is almost always unique. It also is non-iterative, namely we get just one chance at selecting the "question". As such this is a clear case of information retrieval. It does add the dimension of parsing and syntax analysis.

6. Directed Decision Dynamics

Robotic assembly machines may fit this area. They are directed, they are dynamic, and they must make decisions. For example if we have an assembly line with multiple models of cars, there may be a multiplicity of assembly directions for each model. The robot must identify the car and perhaps even "see" the differences.

7. Undirected Decision Dynamics

Consider a game of cards, a random game of cards. Namely when the deal changes so too may the game. Five card stud and so forth may be chosen. Thus every time a new game starts the system must first ascertain what the game is and then learn it and then play it. This area naturally fits into what we have seen for decades as war games. Certain centers such as the Naval War College conduct a multiplicity of games to see what scenarios could be presented by a variety of putative adversaries. Then we examine the response and continue the effort. The 1984 movie, War Games is a classic initial presentation of taking this simulation approach, placing the "rules" on a computer, and hen taking the "human" out of the loop. War Games are a classic example of undirected decision dynamics. We do not know the game the adversary is playing and the only way to asses this is sampling highly uncertain information, possibly taking some action to see the response and then redirecting our efforts according to some overall metric of success.

The 1950-1970 period laid out a multiplicity of War Game Scenarios in a nuclear environment. Survival of a limited number of humans capable of reproducing was the acceptable end point. The destruction of society and billions was acceptable. Until some started to think a bit about this "mutual assured destruction" approach. Taking the "Games" and placing them on a computer would be the ultimate enablement of an undirected dynamic decision AI system. One would suspect that perhaps as in the film the ultimate decision is "not to play the game".

Now a recent case which may fit this scenario is that of the self-driving car. At best we may tell the vehicle the desired end point. We could equally ask the vehicle to take us to view the Fall

foliage in New England, thus creating a second layer of vagueness but with some modicum of specificity.

8. Thinking

What is thinking. Does it mean I can write a poem? Write a short story. Devise a new algorithm or find a new chemical pathway or genetic pathway? Can some AI system develop a new philosophical approach, say aligning Wittgenstein and Heidegger? These become complex and beyond what may appear today.

However when we examine the machines that think which Gerrish describes we find a set of common threads.

1. Directed

All of the examples are task directed. They drive a car, play a game, work a test, and even may diagnose a disease. They are not general in any way.

2. Trained

They all get trained to do a task. Their advantage is the ability to look ahead but along the path already that they were trained upon.

3. Bounded

Each approach is limited to the task at hand and cannot readily or possibly at all be used for even a moderately different task. The machine plays Go, Chess, Atari Games, but cannot go laterally to another game.

4. Common Techniques

Whether we call it deep learning, neural nets, hidden Markov models or whatever, there are some common methodologies that enable the directed and learning to get the systems to maximize their performance. Driving a car has two objectives; get to where you want, and do so in a harmless a manner as possible. There is a path and there are exogeneous limitations.

Thus, AI, as a broad rubric, can be understood as such, yet fails to achieve what we saw a century ago in radio design for example. It is not a cohesive systematic body of knowledge. It is a collection of the proverbial silos, many using similar techniques, yet each optimized for their separate and special use.

Thus the question we may pose in the context of the current discussion is as follows: can we use data from a cross section of non-invasive methodologies in such a manner as to equal or exceed the diagnostic capability of classic histo-pathological techniques? My opinion currently is; it is an open question, but worthy of consideration.

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