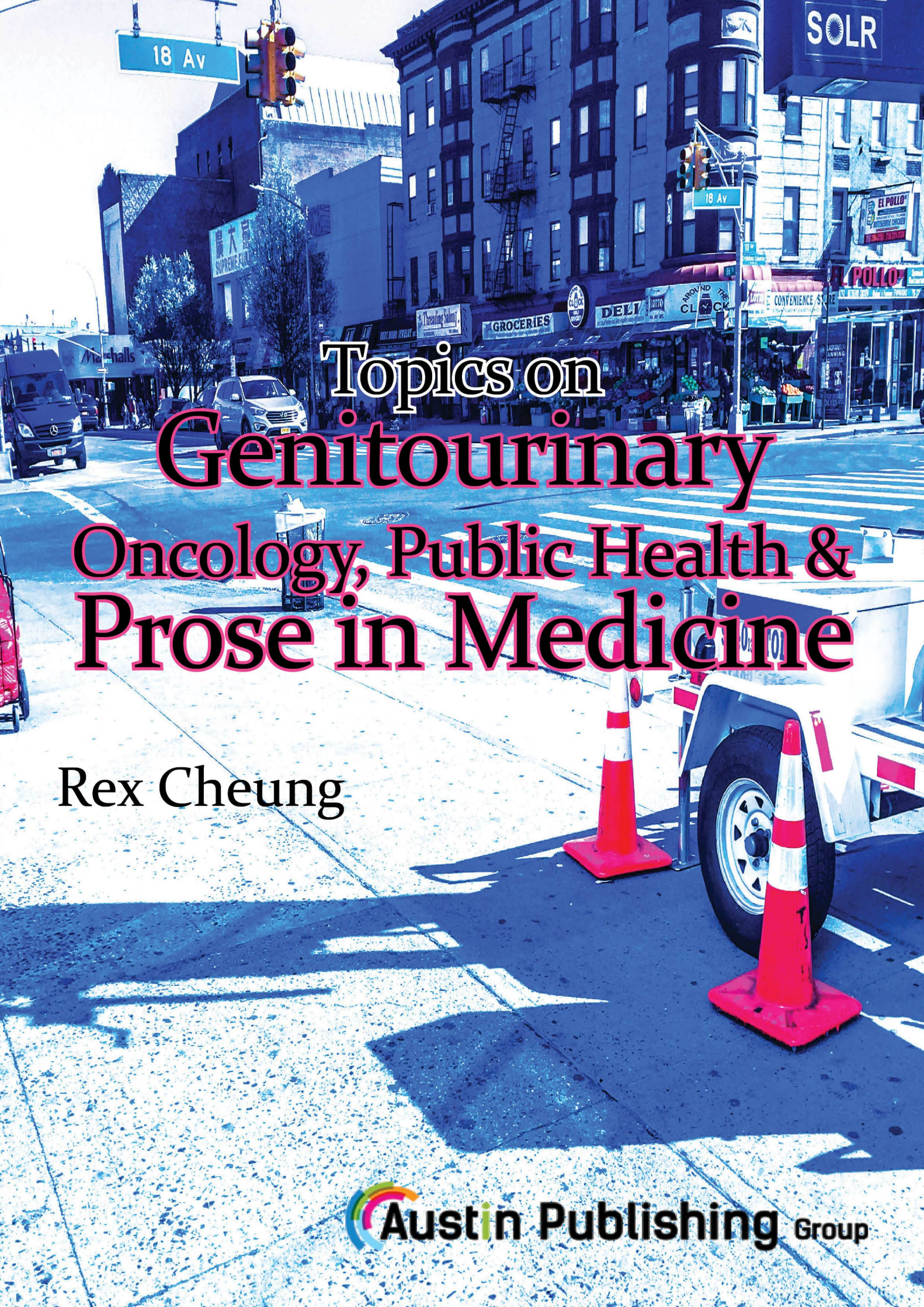

Topics on Genitourinary Oncology, Public Health & Prose in Medicine

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Austin Publishing Group

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Prologue

My Brooklyn in November: version 1.

This is the final book of a series of 10 books discussing the challenges facing modern oncology, climate change, pollution, and public health; and prose in medicine. This book focuses on cancer genomic and public health related to genitourinary oncology. This book covers the modern aspects of radiation oncology such as stereotactic body radiotherapy (SBRT) and the various levels of radiotherapy technology that are useful in clinics of various regions. Like William Carlos Williams, I have a long interest in using prose to portray my neighborhoods and beautify them: Yates said to lift up a community say nice things about it. Community is a place where we rest and regenerate, and important for public health. This book may be useful for oncology and public health practitioners and researchers. C@Brooklyn, 1.23.2016.

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Chapter - 2

The 123 Fundamentals of Maintaining the Health of an Immigrant Community

I arrived here about 25 years ago in Brooklyn and have a particular interest in immigrant health. Immigrants came here to freedom [1] and the simplicity of open sky American [2], security of law, food and work, and no ordinary opportunities for their children in my azure blue Brooklyn harbor town [3-10], many away from the heavily polluted Asia Pacific region and undemocratic societies [7,11-16]; like the new immigrants moved into Paterson New Jersey of William Carlos Williams 1930s great depression time [17,18]. Brooklyn is a historic town, its 14th Brooklyn was part of Lincoln's regimen during the civil war in 1860s [19]. In my fishermen town Brooklyn, you could eat seafood such as the ethnic sushi and sashimi that are good to the cardiac health; on New Year's Eve, there are empty crab and lobster shells cooked with spicy scallions left on the dinner tables, no empty chairs: symbols of an abundant new year celebrations. My favorite sushi chefs are like ninjas in disguise hiding in their castles with supreme culinary skills and a natural control over the elements for authentic sushi [20]. Some 260000 Asian American neighbors old and young would receive their New Year's coveted heartwarming news from their homeland; the news would start from one meeting place in a restaurant and echoes like a tsunami in Brooklyn to the other restaurants, laundry shops, grocery shops, bakery shops, pizza shops, or bagel shops, with sometimes unpredictable impacts on their psychology [21-23]; three buses heading down the road in this cold winter, but spring will roll into my Brooklyn again in April.

With internet, the results of government funded projects, for example of a recent drug used for heart attack prevention and treatment could be disseminated to the public as soon as possible for public health and safety [24]. With modern technology, once properly educated about the values and methodology of public health, social media could be used to mobilize and organize neighbors for public health education and efforts [25]. Some culture [26] believes there is no cure for cancers especially aggressive lung cancers and they do not seek the correct therapy even with painful metastasis but rather delaying the treatments for the deadly cancer and spending time on trips to have some fun or simply move back to their homeland, which is understandable, but often not knowing there are modern treatments even for cure: I found education of the neighborhood is important for public health.

In my Brooklyn New York, we have the bluegrass Appalachian folk music [27], and we have a marine climate [28] because we face the Atlantic Ocean that is the 2nd largest ocean covering 20% of earth surface [29]. My neighborhood is south Brooklyn could be qualified for a fishing town where people would dry their fish outside their windows. The life near the Brooklyn harbor has been celebrated by Bishop [30,31]. We sometimes want to be like her [32], and in a fast New York hour became one. Our Brooklyn has many tall and heroic tales that move us to tears and reminds us the importance of one person in our chase to free global socioeconomic disparities [33-36]. These understandings are important for communication and harmony in this multi-ethnic country, sometimes because of different sensibilities, communication could be challenging in a multi-cultural community quite typical of my land Brooklyn [7,8,37]. I have also always wanted to write about the Texas Gulf region since 2008, but for 8 years I am procrastinating like the Egyptian writer sitting in Nile Delta occupying his lazy times waiting forever for the productive tomorrow to come and how to stop time [38]. Although I do have to watch my toes gingerly walking in my multi-ethnic community, many residents here wear many kinds of hats watching out for each other; there are construction workers, officers, flower shop sellers, and the detectives for significant stories; there is enthusiastic volunteerism and sometimes feel like a very treacherous but funny war zone with diverse sensibilities and great stories [39,40]. Instead of mumbles and jumbles that everyone could hear anyway, you may as well say it the country you love and return to, like Ernst Hemingway said probably while he was in the Florida keys, where he thought about what he had and not had [41,42]; like Hemingway said, waitresses, and I think waiters too, were the most patriotic!

Sometimes, immigrants may feel working in a dead end mouse trap with cheese for financial reasons, like the Disney fairy tale story of Mickey mouse first appeared on November 18, 1928 [43] around the great depression of U.S. created by an cartoonist born in Chicago by an Irish Canadian father and a German mother [44]; when they have the free time, they would spend eating some grapes on porcelain plates hiding under the trees from the California sun reading ethnic newspapers; and some relax at the Brooklyn harbor. Sometimes I would go out into 3 or 4 shops to sample what concerns my neighbors the most, and write them down on my little cell phone computer. Sometimes neighbors are misguided about the importance of one person's health, in democracy, no one should be left out from the efforts of improving public health; that requires some reminding and education. In a neighborhood restaurant, a waitress crossed her arms over her chest, standing over a family of customers tending her customers at one of our buffet restaurants. From restaurants to restaurants and shops to shops, immigrants open their hearts to their customers and one another and do all they can to serve the local community. In my land Brooklyn, each of us believe we could make a difference; neighbors sometimes sit around in a tea house to think and talk about their daily challenges and their fight to have a better community, and yearning in their tantalizing memories while chewing on their favorite food: what about this and what about that kind of discussion, and what they could request their community leaders to improve the quality and fairness of health care.

There is a vacuum after the colonial powers retreated from Asia such as India, Burma and special administrative region Hong Kong China, while some commonwealth states continues to thrive to date [45-48]. Like in America, early significant medical and other advances had come from Europe [49]. The first appendectomy was performed in 1735 in London by British and French cooperation, the first patient recovered magnificently in one month [50]. Now public health advances, prevention and control of epidemic most rely on international cooperation [51,52]. New Chinese American immigrants intoxicated by the coveted music, a medicinal physic, wild beneath a calm and clean porcelain surface, with promises of memories, riches and loves. Although they do prefer the newspapers here not used for only propaganda of their governments. I live on a historic street in my Brooklyn neighborhood, in May, cap and gown would line up in front of cameras taking nice pictures under the waving tress away shielding them from the California sun. Fish is popular here, could be from local catch or from another state [53], and the local taste is multi-ethnic ; the other night, I saw a neighbor enjoyed a seafood in an Indian American restaurant, said sit closer, with her tall and handsome mate celebrating the New Year; made a wish for a monumental year in 2016 in global cancer prevention and control.

In my multi-ethnic Brooklyn, there are cultural monuments and protocols our neighbors execute precisely, open their arms and hearts, in the old memory of their lives in their fatherland during the New Year celebration, for Chinese Americans some celebrate with their good fortune to be here and together enjoy the tantalizing mulan flowers in porcelain vases and lobsters on china plates: two ways to treat their homesickness and the longings for re-uniting with their loved ones [54] and to move beyond past pains [55-57]. In Milwaukee, my genuinely happy friends celebrate with wines and cheeses [58]. Things could be so easy here, sometimes I take things for granted.

Many Asian American immigrants here rely on its own community and their homeland for spirituality and doing business. It is the love of our community, when our democracy is mobilized, we tend to cover our community every well with our own initiatives to prevent and control the perils to our public health. In public health, there is a 5% chance based on a two tailed model on a bell curve attributed to God's chance [59], In many cultures, humans pick a lucky date to do certain things to get that 5% to complete the 95% determined by hard work and diligence: to get the almost entire 100% chance of success.

America is home to many immigrants seeking a free and egalitarian society ernestly chasing dreams and our free culture [3,41,60-62] and I think my land Brooklyn is the most beautiful land, many here start from humble beginnings [63,64]. Lincoln has long been the symbol of American greatness, ideals, power of democracy and patriotism [3]. The infamous Carmen [65] is a Romani women from the Himalaya [66] north of India [67], where 9 out of 10 are world mountain summits are; she and her husband Jose would have also wanted to start their honest new life in the America. There are about one million Romani people live in American including the temperate semi-deserts in California north of Mexico, and Texas [68]. My Brooklyn neighborhood actively participates in our community health and takes pride in it: it is as easy as counting 123 of the Himalayas mountain tops.

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Chapter - 3

Topics of Genitourinary Oncology, Genomics and Public Health

INTRODUCTION

This book is a part of a series of books discussing the challenges facing modern oncology and public health [1-8]. Recent advances in cancer genomics have provided a way to innovate on targeted systemic therapy and advances in computing and technology have allowed robotic stereotactic radiosurgery (SRS) and body radiotherapy (SBRT), these will improve the outcome of cancer treatment and decrease treatment toxicities [9]. Public health barriers could be significant for patients to receive best treatments because of disparities in socioeconomic status (SES) in U.S. and some of the developing countries may be have the most advanced technologies [4,9,10]. Studies using various stages of radiotherapy technologies will be discussed as globally any of these technologies may still be in use [11,12]. Pollution and climate change has emerged as a global threat to public health [13,14]. To improve community health, clear education and communication of the neighbors are important [15- 18]. This chapter will discuss selected topics of cancer genomics, public health, and the effects of food and nutrition, climate change and pollution related to oncology and genitourinary cancers [19,20].

PROSTATE CANCER GENOMICS AND METHODOLOGY

In the PSA era, localized prostate cancers are highly curable with surgery or radiation with or without androgen suppression [12,21,22]. There are about 32000 prostate cancer patients with castrate resistance disease die annually [23]. Metastatic prostate cancer has been treated with androgen deprivation (castration) therapy effective to decrease serum testosterone level to < 50 ng/dL for > 60 years; the prostate cancer eventually progresses to castrate resistant prostate cancer (CRPC) [23], but actually remain very sensitive to intra-tumoral hormone [24]. Androgen receptor (AR) [25] is a quintessential pharmaceutical molecular target in overcoming hormone resistance in CRPC [24]. Cancer genomics will provide the framework to develop target therapy for cancer patients [26-31].

In this 2009 paper, the investigators reviewed the remedies for castrate resistant metastatic prostate cancer [24]. ETS (E26 or E-twenty six) is a family of the hairpin helix-turn-helix DNA control molecules [32] that encodes a 135000 molecular weight gag-related protein p135; E26 (p135) has three element linked together: 5' delta gag-mybE-ETS 3' [24,33]. The ETS group has 9 genes in Drosophila fruit fly, 10 in C. elegans, 28 in mice and 29 in humans [32]. The increased sensitivity of prostate cancers to hormone is secondary to androgen receptor mutation or amplification [24]. Intra-tumoral increased level of androgenic steroids could come from increased conversion of serum adrenal androstenedione testosterone or from de novo synthesis from cholesterol and progesterone [24]. CYP17 is a key enzyme in steroid synthesis in prostate cancer, non-specific inhibitor ketoconazole at concentration (> 800 mg/day) [34] several times higher than anti-fungal dosage is limited by about 30% treatment limiting hepatotoxicity [24].

CYP17A1 (cytochrome P450 superfamily 17A1) has 17 alpha monohydroxylase activity that puts an OH group on the steroid D ring; and 17,20 lyase activity that cleave side chain off the nucleus by hydrolysis of the C-C bond; it is a key enzyme located in endoplasmic reticulum for steroid hormone synthesis including androgens and estrogens [35]. Based on molecular modeling, the investigators found CYP17A1 as a triangular prism with edge of about 55 A and thickness of about 37 A [36]. Using molecular dynamics, the study found the anti-androgen abiraterone docks at the binding site similar to the natural substrate pregnenolone, and the model was confirmed by site directed mutagenesis [36].

The abiraterone acetate decreases serum adrenal and intra-tumoral androgens by inhibiting DHEA synthesis [24].

In this paper, the investigators included 50 patients with metastatic hormone resistant prostate cancer [37]. In the phase 2 study, the defined objective response based on RECIST 1.1 [1,38,39], 50% reduction in prostate antigen (PSA) reduction, or circulating tumor cells decreased from > 5 cells per 7.5 ml blood to < 5 [37]. In the study, the patients must be > 14 days from major surgery and chemotherapy, and the residual side effects should be < grade 1 [37]. Circulating tumor cells (CTC) are being investigated as surrogate end points for prostate cancer outcome since PSA level is hormone dependent in addition to the amount of prostate cancer cells present [24].

In the study, the DNA repair genes included BRCA1 and BRCA2, ATM (ataxia telangiectasis mutated, activated by double stranded DNA breaks [40]), Fanconi's anemia (DNA repair genetic defects, 90% develop bone marrow failure [41]) genes and CHEK2 (checkpoint kinase 2 [42]) genes. Olaparib is a poly adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitor that inhibits ovarian, breast and prostate cancers with BRCA 1 and 2 mutations with increased dependence on PARP for DNA repair [37,43].

In this study, the investigators used the prostate cancer working group 2 (PCWG2) criteria [44] and defined PSA progression as rising PSA > 25% at least 1 week apart, soft tissue progression

by RECIST 1.1 or > 2 new lesions on bone scans [37]. The study required patients to have life expectancy > 12 weeks, Eastern Cooperative Oncology Group (ECOG) Performance Status of < 2 (< 50% time in bed) or Karnofsky Performance Status > 50% (requires considerable assistance and frequent medical care) [45], agreed to continue to use contraception for 3 months after finishing the drug, and < 50 ng/dL castrate level of testosterone [37]. The investigators used the Common Terminology Criteria of Adverse Events (CTCAE 4.0) to grade 1 to 5 treatment side effects: grade 1 no to mild symptoms, clinical or radiographic observations and requires no intervention to grade 5 treatment related death [37].

Mutations in AR, ETS, TP53 and PTEN occur in about 40% to 60% metastatic hormone refractory prostate cancer cases, and BRCA1, BRCA2 and ATM in 19.3%, 8% with actionable germline mutations, and 89% of the patients had actionable genetic aberrations [46]. In the 2015 study, the investigators used their institutional clinical sequencing framework for precision medicine [46] to study cancer using next generation whole exome sequencing and transcriptome study using fresh frozen tumor biopsy DNA, and germline whole exome sequencing using saliva sample DNA [23,37,46]. In the year of monumental 1977 for gene sequencing, the Sanger method could only sequence 1000 base pairs annually, and would have taken one million years per human genome [1,11,47]. Next generation sequencing remove the time consuming and labor intensive step of electrophoresis and uses real-time firefly luciferase monitoring of base by base DNA polymerase reaction with a single strand DNA template [48].

In the study, the investigators enriched the targets by cloned DNA libraries using GeneRead DNAseq Panels (QIAGEN formed in 1984, developed, very important for public health, one of the first molecular diagnostic for H1N1 swine flu epidemic [49,50]) on targeted genome sequencing using MiSeq sequencer (Illumina [51]), copy number data by QX100 Droplet Digital PCR System (Bio- Rad), circulating tumor cell count (CTC) [37,52] by CellSearch (Janssen Diagnostics [53]). For metastatic castration resistant prostate cancer patients, who had docetaxel treatment, treated with steroidal anti-androgen abiraterone [54] and prednisone versus prednisone, 2 year survival for patients with CTC less than 5 circulating cells/7.5 mL blood was 46% versus 2% for 5 cells or more and lactate dehydrogenase (LDH) > 250 U/L [52]. In this study, the investigators classify the patients as biomarker-positive for genomic defects in DNA repair genes if there are homozygous deletion or deleterious mutation in genes related to DNA repair genes or PARP inhibitor sensitivity [37].

In 1953, Watson and Crick published the double helix model of deoxyribonucleic acid (DNA), complimentary strands of bases adenosine (A), cytosine (C), guanine (G) and thymine (T), at Cold Spring Harbor Symposium [55]; and 1958 DNA was found to be the genetic codes for protein synthesis; Symposium Cold Spring Harbor, a hamlet in the Suffolk County on U.S. route 25A on the North Shore of Long Island, a whaling town declined in 1860s next to sailing resort Long Island Sound and now a popular scenic residential community of global NYC [56,57].

In the study, the patients had 400 mg twice a day PARP olaparib, all had previous docetaxel chemotherapy, 98% had abiraterone or enzalutamide, and 58% had cabazitaxel, 33% had an objective response, 12 patients had more than 6 months treatment, 88% of patients who had DNA repair gene mutations or deletions had a response [37]. The investigators had seven of the responders had BRCA2 loss and 4 had ATM aberrations [37]. In the study, 20% had grade 3 or 4 anemia or fatigue [37].

In this paper, the investigators 426 localized prostate cancer patients to study how cancer genomic related to 2005 International Society of Urological Pathology (ISUP) Gleason score [58]. Gleason score (pattern) [58,59]: from well differentiated to poorly differentiated: 1 for small well differentiated uniform glands, 2 with more stroma between glands, 3 with distinctly infiltrative margins, 4 irregular mass of cancer, and 5 with occasional poorly formed glands or only sheets of cells in anaplastic prostate cancer [60]. The final Gleason score equal to the Gleason score of the major and the minor patterns [60]. In 2005, ISUP modified the Gleason groups: I for < 6, II 3+4 = 7, III 4+3 = 7, IV 8 and V for 9-10 [60]. In the paper, the study used whole exome and genome sequencing found Gleason (PG) group I to III are distinctive genomic diseases and IV and V are the same disease at the genomic level [58]. The study found no polyploidy in PG grade I, there were 1.3% in grade 2, 3.1% in grade 3, 3.5% in grade 4 and about 9% in grade 5 [58]. The investigators studied 900 cancer genes, about 400 were amplified genes, and increased amplification with increasing PG [58].

In this study, c-Myc copy number aberrations are the most significant reaching about 45.5% for PG grade 1, 13.6% for N-Myc, and 6.8% of L-Myc [58]. Myc associated factor x (MAX) [61] binds members of Myc family of cell growth and cell cycle proteins, the dimerized form binds to the basic region of the E-box DNA sequence and recruit histone acetyltransferases [62-65]. C-Myc is homolog of v- Myc viral oncogene that was isolated from domestic fowl with spontaneous myelocytomatosis, MC29, in 1964 [66,67]. In human c-Myc is located on chromosome 8 and regulates about 15% of human gene, important for cell cycle G0 to G1 transition [62,68]; N-Myc is also the hairpin helix-loop-helix protein 37 interacts with aurora A important in cell cycles during normal brain development and central nervous system (CNS) carcinogenesis, and L-Myc gene is MYCL1 [62-65,69,70]. The study found several recurrent mutations in hormone naïve prostate cancer, only TP53 increases with PG: grade 1 0%, grade 2 7%, grade 3 8%, grade 4 10% and grade 5 9% [58].

In this paper, the investigators included 7869 prostate cancer patients underwent radical prostatectomy from 1982 to 2011 with Johns Hopkins Radical Prostatectomy Database [71]. In the study, after a median follow up of 2 (range 2 to 11) years, the 5 year PSA outcome was 94.6%, 82.7%, 65.1%, 63.1% and 34.5% for biopsy Gleason groups I to V respectively and for prostatectomy groups 96.6%, 88.1%, 69.7%, 63.7% and 34.5% respectively [71]. With modern tissue staining and immunohistochemistry techniques, Gleason less than 6 is extremely rare [58].

In this paper, there were 5205 patients with biopsy Gleason score < 6, one had a Gleason 4 and 7 with Gleason 5, and 99.8% had Gleason 6 [71]. For 3548 men with prostatectomy Gleason score < 6, 1 had Gleason 4 and 44 had Gleason 5, and 98.7% had Gleason 6 [71].

In this paper, the investigators profiled the kinome related to AR [72]. The studied in details the human choline kinase alpha (CHKA) cloned in 1992 by complementation of the yeast choline kinase and a human brain tumor cDNA library [72-75]. Kinome includes a family of protein kinases phosphorylate amino acid residues serine, threonine and tyrosine; kinome was first described in 2002 on 518 human kinases [76,77]. In the paper, the investigators studied CHKA expression in 195 benign, 153 prostatic intraepithelial neoplasm, and 359 prostate cancer lesions using RNA sequencing of prostate cancer transcriptome [72]. The investigators found CHKA, a potential therapeutic target, as the first chaperone of AR by enhancing the stability of the molecule [72].

AR interacts with other transcription factors such as FOXA1 [78], OCT1 [79] and ETS family members [32,80]. In human, runt related transcription factor RUNX1 gene is on chromosome 21, it has 12 exons, 260 kilobases and 2 enhencers; it regulates the differentiation of blood cells [80,81]. In this paper, the investigators studied the epigenetic modification of RUNX1 histones and the relationship to prostate cancer using cell lines [80]. Histone methylation has been related to normal central nervous system development, associated with long-term memory and learning, aging, and neurocognitive disability; trimethylation of histone 3 lysine 4 (H3K4me2) increases in the hippocampus of rats after one hour of fear conditioning [80,82,83]. Epigenetics has been shown to be important in oncology [80,84-86].

In the paper, the investigators used prostate cancer cell lines and reagents (ATCC [87]), antibodies for RUNX1 and EZH2 (abcam, Cambridge UK [88]), small RNAi [89] for RUNX1 for mRNA expression experiments, the Myc-tagged RUNX1 was cloned for enrichment, ChIP-seq technique to sequence the DNA at the binding sites [90,91], western immunoprecipitation blot gel analysis was performed for AR and Myc proteins, the 19 base primer for the qRT-PCR [92]: forward ACTTCCTCTGCTCCGTGCT: and reverse, the study used the GeneChip® Human Exon 1.0 ST Array [93] for expression microarrays [91]; the study also included 103 human prostate cancer samples of prostatectomy from University of Tokyo was used in immunohistochemistry study of EZH2 gene expression [80]. In the study, the investigators concluded that AR and EZH2 drives the RUNX1 and[80] RUNX1 was important in progression of prostate cancer to the androgen refractory stage [80].

URINARY BLADDER CANCER, EPIDEMIOLOGY AND GENOMICS

Urinary bladder is a hollow organ; bladder cancer (BC) is a cancer of the urothelium, most common type transitional cell carcinoma; in U.S., the 5-year survival rate of bladder cancer is about 77% [94], non-invasive for 90%, invasive for about 60% [95], < 10% for metastatic BC [96]. Transitional cell carcinoma (TCC) also occur in 5 to 10% of renal cancers; its most frequent site of extrapelvic metastasis is bone and about half of these is in spine [97,98]. The etiology of BC

included age, smoking, pollution and bladder infection [96]. About 0.5 of population attributable risk (PAR) of BC is due to smoking in U.S. [99]. From a meta-analysis of 43 studies, the summary odds ratio for current cigarette smokers versus non-smokers was 3.33 and for former smokers was 1.98 [100]. There was a four times increase in male to female partially because of smoking [101]. 70% of BC are non-muscle invasive Ta and T1 that are treated with transurethral resection of the bladder tumor (TURBT) may be followed by adjuvant chemotherapy or Bacillus Calmette-Guerin (BCG) immunotherapy producing local infection and anti-tumor inflammatory response; radical cystectomy are usually followed by chemotherapy methotrexate, cisplatin, vinblastine and doxorubicin (MVAC) or carboplatin and gemcitabine [96].

The BCG vaccination is a great public health success story in preventing human tuberculosis, it started in 1854 when bovine tuberculosis was discovered, after 13 years of culturing and attenuation of the BCG strain, in 1919 it was found to be safe for research animals and in 1921 it was used for humans, and it costs 16 cents a dose in 2014: it is on the World Health Organization (WHO) list of essential medicines for keeping basic good health [102].

In this paper, the investigators from Kagoshima and Chiba Japan included 83 (58 bladder cancer (BC) and 25 normal bladder) specimens from Kagoshima University Hospital to study the genomic of bladder cancer [95]. Kagoshima, also called Naple of the East, at southern most of Japan (31oN) is famed for fried fish cakes and has a subtropical climate [103]. Chiba is the 6th most populated prefecture, 27th by land area of the Tokyo and surrounding areas, with some landfill from sands of the Tokyo Bay, it produces sushi nori and flavoring mirin, soy sauce and sake, and it is a modern industrial and medical city [104,105]. In this paper, the investigators studied the RNA transcriptomic of non coding RNA [95]: a genetic operating system [106]. In this futuristic 2004 paper, it discussed the microRNAs (miRNA), about 22 nucleotides, as a novel genetic control played a regulatory roles of mRNA [107]. The investigators studied miR-23b/27b angiogenesis related miRNA cluster [108]; the investigators extracted RNA from clinical samples, transfected BC by miR-23b/27b RNA and found the miR23b/27b inhibited BC migration and invasion [95].

In this paper, the investigators identified epidermal growth factor receptor (EGFR, HER1 [109]) and hepatocyte growth factor receptor (c-Met [110]) are targets of miR-23b and miR-27b RNA [95]. The study found miR23b/27b cluster regulated the levels of EGFR and c-Met proteins from the activity of the activity of a reporter Renilla luciferase [111] expressed only when the inserted EGFR or c- MET was expressed and normalized over an always expressed firefly luciferase to control for the natural variability of the samples and western blot. The study found miR23b and miR27b RNAs suppressed bladder cancer carcinogenesis and metastasis [95].

In this paper, the authors from Madrid Spain reviewed the importance of EZH2 (Enhancer Zeste Homolog 2) in BC carcinogenesis [96]. Madrid, originated from the Matrice river crossed its initial place of settlement, is the capital of Spain and a major medical city, its population stabilized at about 3 million in 1970s, because of its altitude (667m, 40oN3oW) it has a dry and

hot climate (had the hottest temperature on July 24, 1995 at 108oF), and has the among the lowest precipitation in Europe [112], the tallest skyscraper Torre Picasso next the Pablo Picasso square stands 157 m [113], Madrid's climate is similar to semi-desert and desert Utah where Spanish explored in 1500s in U.S. [114]. Polycomb (Pc) was initially a mutant gene for improper body segmentation of Drosophila fruit fly by regulating the homeotic genes [115,116]; it was later found a epigenetic silencer gene regulator of many cancers [117]. Pc proteins are divided into Polycomb repressive complexes 1 and 2 (PRC1 and PRC2); EZH2 is the catalytic core of PRC2 epigenetically silence several tumor suppressor genes by trimethylation of histone 3 (H3) at lysine 27 (K27) position: the docking site for DNA methyltransferases and histone deacetylases [118]: EZH2 overexpression is associated with several cancers including BC [96].

In this paper, the investigators studied HER2 as molecular targets for treating urothelial cancer [119]. HER2, also called HER2/neu or erbB, is an important biomarker and molecular target for about 30% of breast cancer patients [120]. HER2 is over-expressed in 6% to 80% of UC patients [119,121,122]. The investigators included 111 patients from Spain and 102 from Greece with metastatic urothelial cancer/bladder cancer (UC/BC) treated with platinum based chemotherapy [119]. The study used immunohistochemistry (IHC), florescence in situ hybridization (FISH), DNA copy number, mRNA expression and mutation profile to related HER2 status to overall survival (OS) of UC patients [119]. FISH is a genetic test of finding and labeling cells with complimentary DNA sequence on the chromosomes [123]; and IHC finds the complimentary binding sites on antigens to a antibody, and the molecular interaction could then be imaged [124]. The investigators found 2% HER2 mutations, 22% of Spanish patients had 3+ HER staining versus 4% for Greek, 20% of Spanish patients had FISH amplification versus 4% for Greek, and HER2 status was not associated with OS of UC patients [119].

In this paper, the investigators study the relationship between metabolic syndrome (MetS) and urothelial carcinoma of bladder (UC/BC) [125]. The investigators included 690 patients with UC/BC in Italy and 665 without UC/BC as controls from 2003 to 2004; MetS was defined as have ¾ of: abdominal obesity, hypercholesterolemia, hypertension and diabetes [125]. The study found the odds ratio (ORs) for UC/BC: MetS 2 times increased, 2.20 for diabetes, 0.88 for hypertension, 1.16 for hypercholemia and 1.63 for abdominal obesity; a significant 8.1% of UC/BC was attributed to UC/BC; this confirm other study the importance of increasing rate of obesity and MetS on outcome of UC/BC [125,126].

DIET AND GENOMICS

In this paper, the investigators reviewed the human cancer structural and numerical genomic stability closely related to food consumption [127]. Mutational studies by X-rays using Zea Mays [128] found the ends of a mutant or ringed chromosome ruptured in cross over during mitosis determine chromosome integrity [129]. Later DNA replication was found to be incomplete at the ends each time at the end structure telomere, the telomere is a repeating structure and

shorten about 100 base pairs per cell replication [130], it is repaired by telomerase for stability of the genome, and mindful meditation could help to preserve the telomeres [127,131-133]. The telomere prevent damaged DNA ends from unexpected nonhomologous end joining or homologous recombination [134,135]. The correlation between abnormal centrosome and chromosome numbers runs back over a century and may be a cause of genomic instability [136,137]. For cells with mutations of tumor suppressor protein TP53, the cells may escape the cells division checkpoint and have two sets of centromeres and chromosomes (tetraploidy) [138], and may be subsequent more harmful aneuploidy with chromosome number different from the normal 46 chromosomes in human [127,139].

In this paper, the authors discussed the recent nutrigenomics studies have found a close relation between food and genomic stability [127,140]. A well known Agouti gene is related to coat color in mammals [127]; Agouti mutation in mice is associated with increased risk for cancer and obesity of offspring, but feeding pregnant mice with folate would reverse the hypomethylation of the Agouti gene [127]. In 1920s, folate deficiency was found to cause anemia [141]. In 1930s, it was found brewer's yeast (e.g. ale yeast and baking yeast) contains rich amount of minerals and B vitamins except B12 could treat anemia [142]. Folate is essential in DNA and RNA synthesis by one carbon metabolism of ring closure in purine synthesis [141,143]. In U.S. grain products are fortified with folic acid to improve public health [141].

CLIMATE CHANGE AND CANCER MORTALITY

In this paper, the investigators from Madrid Spain used clinical data from National Institute of Statistics and climate data from National Institute of Meteorology to study the effects of temperature, rainfall and annual number of sunshine hours on the mortality of prostate cancer using the Martonne Index [144]. Martonne published a study about the about 750 miles Alps in 1926 using the index of Martonne [145-147]. The study used the Martonne aridity index (AI) as the quotient of annual rainfall and mean annual temperature plus 10 oC: extremely arid zone as below 5, 5 to 15 as arid zone, 15 to 20 as semi-arid zone, 20 to 30 as subhumid, 30 to 60 as humid and over 60 as superhumid [144]. In the study, the investigators hypothesized prostate cancer mortality may decrease with increased sunlight because of increased vitamin D synthesis [144,148]. The study found higher prostate cancer mortality with higher Martonne AI, lower in areas with increased number of sunshine per year, and there were 21.51 cases per 100000 males years in extremely arid zones and 35.87 for humid zones [144]. The authors suggested a link between cancer mortality and climate change but advised caution in interpreting data [144].

Aridity index is useful in climate change studies and classifying world climate. For example, in most of U.S. is covered by temperature climate, tropical in Hawaii and south Florida, semi-arid in the great plains and arid in the great basin, because of the population growth California has a mild Mediterranean climate but may face water shortage by 2020 if more supplies are not found [149].

In this paper, the investigators from Lasi Romania included 54 patients borderline ovarian cancer to study the relationship with global radiation, temperature and precipitation of north east Romania [150]. Lasi (also Jassy) is a major medical center and was the capital of Romania from 1916 to 1918, it is a symbol of intellectual and cultural Romania, is related to the Persian Alanic Jassi people; Lasi's monthly precipitation varies between 25 mm in October to 100 mm in June, and the summer temperature could reach 40oC, it has a population of 290422 in 2011 and is the 4th most populous city, 60000 students in 5 public universities, and there are half a million people living in the peri-Lasi area that is situated on seven hills like Rome [151]. In the study, the mean age was 46 years old with 18 serous tumors, 27 mucinous, 8 mixed and 1 Brenner tumor, treated over 22 years from 1988 to 2009 [150]. Based on the times of treatment and distribution of the cases, the investigators concluded that 4.87%, of their 1107 ovarian tumors treated, was lower than expected from literature, and was related to global radiation associated with climate changes [150].

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Chapter - 4

Selected Topics of Radiotherapy of Genitourinary Cancer

INTRODUCTION

This chapter is part of a series of discussion on challenges of modern oncology and public health [1-9]. This chapter will discuss the conventional radiotherapy (RT), 3 dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT) of GU cancer [10-12], the related normal tissue complication probability (NTCP) models [13-15], and systematic treatments of genitourinary (GU) cancers. It will also discuss the public health implications of using advanced technology [16,17] in treatment GU cancers. As clinics in different regions of the world are at different levels of radiotherapy technology development, treatment results using all levels of treatment technology are amazingly helpful [18].

PROSTATE CANCER 3DCRT

In this 2003 paper, the investigators from M.D. Anderson, Houston U.S. included 363 high risk prostate cancer patients treated with 3DCRT to study the effect of radiation dose increase on treatment outcome [10]. Houston is a global medical city, called the space city, of the 3 cities Houston, Sugarland, Woodland and Houston, is the 5th most populated city of U.S.; by 1860, it became the heart of cotton trade; it has a humid subtropical Gulf climate, in June 2001 the worst tropical storm dumped 40 inches on rain on Houston; it is the sister city of Chiba Japan [19]. The study included prostate cancer patients with > 1992 AJCC cT3 on digital rectal examination (DRE), 8 biopsy Gleason Score, and 20 mg/mL PSA [10]. The American Joint Committee on Cancer (AJCC) staging manual is now at 8th edition; AJCC provides evidence based staging, and staging atlas [20]. The study found the tumor control dose at 50% (TCD50) [1,21] was about 76 Gy; the difference in 5-year 's TCD50 at a cut-point of PSA = 20 was about 15 Gy using Martingale analysis; the projected increase in 5 Gy at 5 years in PSA control was 10% [10].

In this 2005 paper, the investigators compare treatment outcome using different PSA failure definitions: 3 rises in PSA [10] versus Phoenix definition (PSA increase > 2 ng/mL [22], also called CN +2 definition) [12]. The study found the TCD50 [1,21] at about 70 Gy; the relative slope of rise at TCD50, r50, was 180 cGy (95% confidence interval: 80 cGy to 280 cGy); at 5 years, using a cut-point of 13 ng/mL, the difference was15 Gy in [10] versus 20 Gy using the Phoenix definition [12]. In this 2008 paper, in numbers, the increase of 8 Gy from 70 Gy to 78 Gy increased the PSA control of about 20% from about 60% to 80% [23].

PROSTATE CANCER IMRT

Prostate cancer is the most common non-skin cancer in Australia and UK, there are respectively about 18000 and 37000 new cases in 2008 [24,25]. In this 2015 paper, the investigators from Coffs Harbour Australia studied using advanced magnetic resonance imaging 1.5 T and 3T endorectal coil MRI (ER MRI) [26] for radiotherapy treatment planning [24]. Coffs Harbour of New South Wales (NSW) is a quaint coastal city of Australia, about 540 kilometers north of Sydney, has a population of about 46000 in 2011, and public passenger NSW TrainLink connect the community to the rest of Australia [27]. In the study, the investigators included 509 prostate cancer patients treated with IMRT over 2 years form 2010 to 2012 to study the ability of MRI in detecting extracapsular extension (ECE), seminal vesicle (SV) invasion and adjacent organ invasion [24]. In the study, 7 of the 509 patients had low risk disease, 255 had intermediate risk disease and 247 had high risk prostate cancer [24,28]. The study found MRI upstaged 20%, moved 9% to a higher risk group; MRI is the main imaging determinant for 18% of the patients; and MRI changed the hormone therapy for 8% of the patients [24].

In the study, the patients were treated with fiducial marker based IGRT [29] cone beam CT and on-line correction; the investigators required 2 months rest between transrectal ultrasound (TRUS) guided prostate biopsy [30], and 2 weeks for fiducial marker implantation [24]. In this prostate cancer screening study in the Netherlands, one week after the prostate biopsy, 2% had prostate pain, 4% fever > 38oC, 7% blood in urine > 1 week, 25% blood in feces, 31% blood in sperm, 4% take pain killers, and only a few percent had side effects interfered with their normal life and sex life [31].

In the study, the investigators treated the patients to 78 Gy in 39 fractions or 81 Gy in 45 fractions, the clinical target volume (CTV) [32] for low risk include the prostate, prostate and 6 – 8 mm of proximal SV for intermediate risk, and for high risk typically also treat the distal SV with simultaneous integrated boost to 56 Gy or 60 Gy; 5 node positive patients had pelvic nodal irradiation; the intermediate risk patients received 4 months of intramuscular (IM) injection of 30 mg of lucrin and also adjuvant 2 years for the high risk patients [24]. Lucrin (leuprorelin) is a luteinizing hormone releasing hormone (LHRH) [33] analog inhibits the pituitary GnRH (gonadotropin releasing hormone) receptor, and decrease gonadotropins and estradiol and testosterone in both males and females [34].

In this 2015 paper, the investigators study the urinary side effects of prostate IMRT and hormone treatment [35]. In the study, the investigators used International Prostate Symptom Score (I-PSS) [36,37] to follow the urinary toxicity of combined prostate cancer treatment [35]; IPSS was developed by American Urological Association (AUA) by extending AUA-7 (7 questions of urinary complaints scaled 1-5) to AUA-8 with 8th urinary complaints related to quality of life scaled 1-6 [35-37]. Nagoya, means peace, is the 3rd largest city in central Japan with 9.10 million residents; at 35oN, it has subtropical climate; it is famous for cotton and complex mechanical dolls [38,39]. In the study, the investigators included 241 prostate cancer with 74 Gy for low risk patients and 78 Gy for intermediate and high risk patients according to National Comprehensive Cancer Network (NCCN), a U.S. network of 25 cancer centers [40], criteria, the investigators did not use whole pelvis radiotherapy [35]. The same group reported the 3 years biochemical disease free survival was 100% for low and intermediate risk groups and 95.8% for the high risk group [41]. After a median follow up of 35 months, the rate of the late grade 2 and 3 gastrointestinal toxicity was 6.6% and 0.8%; and 8.3% and 1.2% respectively for genitourinary side effects [41].

In this study, the median time of neo-adjuvant hormone treatment with LHRH and anti-androgen was 10 months (range 2 to 68 months); the median time of adjuvant hormone treatment, with LHRH alone in 96.8%, was 19 months (range 1 to 37 months) [35]. In the paper, the study found the baseline urinary symptoms were 124 for mild with IPSS 0-7, 70 for moderate with IPSS score 8- 19 and 22 severe with IPSS 20 to 35; at 24 months after IMRT, the average IPSS score of the mild group was 5.1 versus 3.5 for baseline, 10 versus 12.6 for the moderate IPSS group, and 14.4 versus 23.8 for the severe IPSS group [35]. Prostate cancer treatment improved the urinary symptoms.

PROSTATE CANCER IGRT

For IMRT treatment, target alignment using trans-abdominal ultrasound (NOMOS BAT [42]) [43] and in room computed tomography (CT) (EXaCT, Varian Oncology Systems) for image-guide radiotherapy [44,45] directly on the prostate and seminal vesicles (SV) are more accurate dosimetrically than using skin and bone alignments [46]. The study found the prostate coverage was adequate for only 70% using skin and bone alignment methods versus 100% with the CT imaging; for SV coverage 60 Gy or more, only 40% of patients were covered by skin and bone alignments versus 80% with CT [46,47].

In these papers, the investigators studied if ultra tight modern margin of 3 mm was enough for prostate cancer IMRT [48,49]. In the study, the patients were immobilized with reusable nylon and plastic Vac-Log (Med-Tec) [50] from thigh to feet [48]. The investigators included 46 prostate cancer patients treated with 8 fields 75.6 Gy IMRT [48,49]. During an IMRT treatment session of about 21 minutes, the volume of urinary bladder could increase about 127 cubic cm; the mean displacement for prostate was about 1.3 mm (up to 8.4 mm) and 1.2 mm (up to 15.6 mm) for SV, the large displacements were related to amount of rectal gas; and 15% of patients could have

more than 4 mm prostate displacement [49]. In this dosimetric paper, the study found with 3 mm margin only 3 prostates and 8 SVs did not achieve 70 Gy, and hence, 3 mm was adequate for prostate cancer IMRT [48].

SALVAGE RT AFTER RADICAL PROSTATECTOMY

Risk stratification to identify who will benefit from salvage post-prostatectomy is challenging [51]. In this paper, the investigators included 101 prostate cancer patients treated with prostatectomy over 11 years from 1990 to 2001 to study to effect of hormone on salvage treatment [11]. The study found the favorable prognostic factors: favorable group with positive margin and PSA < 0.5 ng/mL versus otherwise; the favorable group has 5 years PSA control of about 84% versus about 61% otherwise and the androgen suppression treatment improved the outcome of the unfavorable group the most [11]. Other investigators have found cut-point of post-prostatectomy PSA of 0.2 ng/mL was prognostic [52]; some investigators have found frailty and older age as poor prognostic factor for toxicity [53].

SBRT AND RE-IRRADIATION

Re-irradiation is challenging because of normal tissue tolerance [21,54]. In this 2014 paper, I reviewed the literature on SBRT of prostate cancer [55]. In this paper discussing 21 years of using biological effective dose (BED), the alpha/beta ratio of prostate cancer is between 1.5 to 3.0 [55,56]. Using fiducial marker based tracking, SBRT could use generally 2 mm to 5 mm tight margin to spare normal tissue toxicities [55,57]. The alpha agonist use for urinary bladder urgency symptoms related to inflammatory response from the SBRT could increase 40% at 18 months, and serious urinary side effect is about 2% [55,58]. The other competing advanced technologies HDR (high dose rate) [59] brachytherapy and proton radiotherapy [60] are being studied [55]. SBRT has be used to treat single lymphadenopathy and single bone metastasis [61] and recurrent prostate cancer [62]. In this paper, the patients with recurrent prostate cancer, had prior RT 45 Gy (range 20 to 96 Gy), with a median size of target of about 35 mm, were re-irradiated with a dose of 36 Gy in 6 fractions over 3 weeks; the local control was about 51% without major side effects [55,63].

BLADDER CANCER IGRT AND IMRT

Bladder cancer (BC) radiotherapy is limited by sensitive normal tissues bowels without image guidance [64,65]. There are limited data on using modern IMRT of bladder cancer [66,67]. In this paper, the investigators studied image guide IMRT of bladder cancer (BC) [68]. In the study, the patients underwent pelvic MRI, had maximum transurethral resection of bladder tumor (TURBT) < 6 weeks before the IMRT, and 3-4 gold markers placed at the tumor bed under general anaesthesia [68]. In the study, the investigators included 28 patients with stage II to IV BC, the gross target volume (GTV) was treated with 66 Gy in 30 fractions and 55 Gy in 20 fractions, GTV expanded 0.5 cm to high risk clinical target volume (CTV), whole bladder was defined as the

intermediate risk CTV and expanded 1 cm to intermediate risk PTV, and when treated uninvolved obturator, internal and external iliac nodes were the low risk CTV and expanded 1 cm to low risk PTV; for simultaneous boost IMRT with 30 fractions, the dose was 66 Gy, 60 Gy and 54 Gy to the high, intermediate and low risk PTV respectively, and 55 Gy, 50 Gy and 45 Gy for the 20 fractions group [68].

In the study, the patients were treated with empty or full bladder was used depending on dosimetry, trans-abdominal ultrasound was used to ensure empty bladder and cone beam CT was used for IGRT [68]. Chemotherapy with 35 mg/m2 once weekly cisplatin was used in appropriate patients [68]. In the study, 6 patients had > acute grade 2 genitourinary toxicity and 6 for acute gastrointestinal toxicity, 5 patients had > grade 2 late genitourinary toxicity and none > grade 2 late gastrointestinal toxicity; 19 patients underwent cystoscopy after IMRT and 16 had complete response [68]. In the study, the results compared favorably with other studies [66,67], for definitive treatment the investigators found overall survival (OS) for chemo-radiotherapy was 100% versus about 70% with RT alone for the BC patients [68].

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Epilogue: Symbolism in Poetry and Medicine

My Brooklyn in November: version 2.

My Brooklyn is Williams Paterson [1,2]: among our immigrants of south Brooklyn, we have the immigrant Shakespeare's European starling Bard's bird originated form South America, first introduced in Central Park New York City, and now there are 200 million starlings spread all over from cold America's north to warm Florida [3].

Life in the developing countries could end around 50s [4,5] too young to develop most cancers. In U.S., the innovation in medical technology has caused the expenses on medical care to increase and cause a concern in public health [6]. Asia is developing rapidly [7,8] with international cooperation on finance and economy [9,10] that will boost Asia's living, democratic [11,12], education [13] and public health standards but challenges remain [14-17]. Improvement in civil rights [18], human rights and living standards [19-21] are essential to improved quality of public

health and medical care but it could take a long time and large efforts; the government health reform of U.S. is an example of progress and could serve as a template to free global population from threatening public health concerns especially in the rapidly developing Asia [22]. Degree of democratic equality and socioeconomic fairness is important for public health, in great depression in U.S. the GDP dropped about a third and unemployment was about a fifth of the full employment, public suffered, he introduced the New Deal based the democratic principle of social justice and improved the public health tremendously [20,23-27].

Here in my multi-ethnic fishermen's south Brooklyn, as the bell rings in the New Year, my neighbors enjoy eating the authentic Japanese seafood in cold New York winter [28,29] from local first fresh catch by local neighbors: my favorites are vinegar radish, avocado, steamed rice, and miso soup for the spirited Asian spicy rolls to prevent heart burns; with warm NYC hospitality, these foods could shake off any loose creases on a face with a longing pain in their chest. If the whole world is a monumental stage, is there anything ever real under the surface [30-32].

It is good time of the year, I saw on television while eating dinner on New Year's Eve, a most beautiful woman put on her most beautiful dress signing the rhymes of the desert [33], seeing her good-looking Sherpa husband to summit Nepal Himalayas [34], north of India. I am excited by my May trip I plan to see Nepal, but first I need to learn about the 123 of the Him-alayas [35]. Human think symbolically, given a symbol human will go through the list of possibilities of meanings in their mind and identify the best ones; I should have known it a lot earlier like in high-school before college; symbols like poetry sometimes are mistaken for being vague, on the contrary, they are limpid and rich in meanings; symbols can bridge the gulf between our existence and our minds; there is symbolism in summiting Him-alayas beyond the 8000 feet (the theoretical oxygen deficient zone) or ice-bergs [36,37]; or facing an the epic storm of 2016 in prospect park of Brooklyn: symbolism is as clear as 123 [38].

After the first snow of 2016 [39] twisted and turned into NYC: C@1.23.2016. 84th Brooklyn.

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