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Contemporary Notes on Public Health and Radiotherapy Topics

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Published by Austin Publications LLC

Published Date: December 02, 2015

Online Edition available at http://austinpublishinggroup.com/ebooks

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Epilogue: Medicine, Public Health and Civil Society in US

A rainbow, around noon time, Brooklyn.

This book is a part of a series discussing important topics posed to radiotherapy in the modern time and the solutions [1-4]. This book concentrates on oncology topics related to public health. There is a chapter in this book on the history of public health in U.S. It has two chapters on gastrointestinal cancers related to diet and pollution that are important in public health [5,6]. There are two chapters compiled and revised from two papers published [6,7], one on selecting the best treatment volumes for radiotherapy and one on the best management for advanced metastatic cancers. There is a note on cancer survivorship to serve as foundation for future discussions and endeavors.

U.S. has come a long way in terms of improving public health. This book will attempt to point out lessons learned from U.S. that could be used to improve the many lives in the developing world. Public health development in U.S., as in the rest of the world, is tied to the development the civic society [8], or a lack of. Given an opportunity, a minority or majority member, driven by an insecurity of human heart and when combined with a sense of impunity, aggression and oppression could occur. As public health policies always have to struggle between public good and individual rights, this is a complex issue to consider. In U.S., after the Second World War, civic society has developed, Jackie Robinson was the first African American hired by the Brooklyn Dodgers, which was the first team formed for this American sport [9]. Civic development, was also part of the march of social and democratic movements in the monumental decade of 1960s [10], has influenced all aspects of civic society in the world such as gender and multi-ethnic equality in US health care [11,12], voting right, secularization of Canadian healthcare, anticorruption campaigns, and gay and lesbian rights [13] and arts [14].

It is interesting to see how a society thrives, and to realized there are invisible forces that bind and test us [15]. I like to write and photograph to show the perennial beauty and melee of my multi-ethnic neighborhoods as I think where we live is important to our wellbeing. I used to live in Lower Manhattan, with many new immigrants, a neighborhood called 5 points full of Shakespearean experiences and traditions in the time of Lincoln [16]. People would come to Lower Manhattan to catch a great deep breath during the weekend, when they could, from the headaches of their shaky busy week; to fish in the tidal waves from the warm tropical currents. Ernest Hemingway [17], once also visited Lower Manhattan, said he liked to pick things that he was familiar with, and obviously important to him to write about. As an immigrant, I have a particular interest in immigrant health care, and finding the barriers to good public and environmental health. Public health in U.S. was started in the "Hell's Kitchen" [18,19] of a crowded neighborhood in Lower Manhattan to improve the poor living conditions of the people lived in the neighborhood, many of them were new immigrants. I have called this series of books and papers the "best of us" [1-4,7,20-25], is a new area to me, I am truly passionate about and will be concentrating on in the future. This book represents my views, not any organization that I may be associated with. I hope to find the "best of us" in treatment, in places, in our spirits and memories that bind us. I like to find the interconnection between arts and medicine. Word of art, sometimes it racks our souls, but it also soothes those are in pains of the purest of hearts. For the best of all of us @Brooklyn 9.9.2015.

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Chapter - 2

History of Public Health in US and Current Initiatives

INTRODUCTION

Public health is an interdisciplinary effort to prevent and control diseases that occur in the population [26]. In U.S., there are U.S. Public Health Services led by the Surgeon General, and Centers for Disease Control and Prevention (CDC) involved in national and international efforts in promoting and implementing public health initiatives [26]. World Health Organization (WHO) is an agency coordinates global public health initiatives [26]. This chapter discusses the evolution of public health in US from a global point of view (POV), is a part of a series of books and papers [1-7,20,27] discussing the problems facing modern medicine and making the best choices on the remedies, to find the best in oncology treatment, in our neighborhoods, our spirits and memories to reduce the burden of pain and suffering of unnecessary death and illness. This chapter selects topics on public health in US and takes a global POV.

PUBLIC HEALTH OF US AND CURRENT INITIATIVES

There has been a consistent march of progress in public health in the last century that has been associated with an improvement of 25 years in life expectancy [28,29]. National disease monitoring was first started in 1850 [28], thus the beginning of public health in US. In 1947, CDC (previously named Communicable Disease Center) was formed to monitor infectious diseases in US, and in 1955 identified poliomyelitis in children vaccinated with one brand of inactivated vaccine, as a result polio vaccination continued with other brands afterwards [28,30]. In US, periodic standardized health surveys was started in 1921 in Hagerstown, Maryland [31]. In 1935, national survey was conducted and resulted in first National Health Survey in US in 1955 [28,31]. These national surveys monitor the major causes of morbidity and mortality, measure the burden of infectious disease, exposure to environmental pollution, and national vaccination coverage in US [28]. In 1930, congress established the National Institutes of Health (NIH) and Food and Drug Administration (FDA) [28]. Public health boards and organizations were created at various levels [28]. In 1931, one fifth of US population was covered by health boards, and by 1950 86% were covered [28].

The 10 areas of public health achievements in the last century included: improved motor vehicle safety, workplace safety, control of infectious disease, a decline of mortality from heart disease and stroke, safer and healthier foods, healthier mothers and babies, family planning, fluoridation of drinking water, and established smoking as a health hazard [28]. Socioeconomic barriers are known to increase morbidity and mortality associated with poor access to health care [1,5,32-39]. Current public health initiative Healthy People 2020 [40,41] includes major goals to promote healthy lifestyle (healthy diets and exercise), control environmental pollution, improve access to health insurance, remove socioeconomic barriers to best health care.

In the early 1900s, in US, many major health problems were associated with infectious disease, poor living condition, poor nutrition and unhealthy habits [28], as in many developing countries today [1,5]. While the incidence of acute diseases decreased, chronic diseases such as cardiovascular disease and cancer increased [28]. Epidemiology provides important quantifying techniques for population science and forms the foundation of public health [2]. For a text on public health see [42], and for epidemiology and biostatistics see [43]. Many of corresponding public health policies used to prevent and control disease in US could be used as a reference point for developing countries to improve health and quality of life [44].

COMPUTER AGE AND PUBLIC HEALTH

The rapid development of the computers and Internet in the 1990s and World Wide Web in 2000s provided a novel way to promote public health and improve communication [45]. Recently, social media has been introduced as a way to connect the community and to promote public health [46,47]. In this 2010 paper, it discusses the usefulness of electronic health records and social media in the improving medical care [48]. With the increased public use of mobile phones and social media, in August of 2009, US government invested 1.2 billion as a part of the American Recovery and Reinvestment Act to promote meaningful use of electronic health records (EHR) for all individuals in 2011 [48]. Social media could connect communities and professionals in remote and rural areas [49], despite some privacy and overuse issues that have dogged the use of social media [50], that may make it a useful tool in the developing countries. Social media could also be an effective way to connect medical professionals to patients with chronic conditions such as Parkinsonism, has been considered as a revolution in medicine in the computer age [51], and Diabetes [52]. The tools that may be used in the online communities may include five important and attractive features for communication: blog, forum, library, chat and wiki [51]. Members could make contributions once a online community manager approved it [51]. Whether the "virtual" communities could contribute to improved population health will need to be a subject of continuing study to further identify their potential deficiencies and possible benefits [47].

SOCIAL SYSTEMS AND PUBLIC HEALTH

Civil society is an important foundation for good public health in U.S. or abroad. For example, after European Springs in 1989 [53], the health care of the Eastern Central Europe has improved because of a transition from a closed society to a democratic society that focuses on individual rights to good health care [8,53-57]. The barriers during the transition were very similar to those of U.S. including unhealthy lifestyle, poor diet (fatty food and not enough exercise), a lack of resources during that time, these conditions have improved with social stability [8,54]. In U.S., Medical Committee for Human Rights improved access to health care to multi-ethnic minorities [11,12]. These civil movements have improved public health around the world.

CONCLUSION

The major challenges in public health, especially related to oncology, will include removing environmental pollution and socioeconomic barriers to the best of health care. In addition to the traditional tools, the use of modern computer technology may provide important contribution to improve social communication and community health and should be further studied. Some of the barriers to health care will be particular to the neighborhoods or ethnicities, and they will require careful attention to the often complex neighborhoods and cultures, to crystalize the understanding of the community, to find the specific needs and remedies, i.e. quantify, model and crystalize the needs and find timely remedies. Heath statistics of local communities in US or abroad could be compared with comparable US data for public health policy considerations.

Brief Notes on Cancer Survivorship

In 2010, there were 1.5 million new cancer cases, and estimated half a million died from cancers [58]. Ageing is expected to increase cancer incidence by 45% in 2030 [58,59]. From 1971 when President Nixon declared war on cancer [60], the mortality rate in 1971 from cancer was 53%, and 37% in 2010 [58]. 328652 were childhood cancer survivors [58]. The expected cancer survivorship in U.S. is about 60% for adults and 80% for children [58]. One of every six persons over 65 years old is expected to be a cancer survivor [58], 61% of cancer survivors are over 65 years old [58]. The most common cancer is U.S. is breast, prostate and colorectal cancers [58,61].

In this 2012 paper, the needs for help on physical, cognitive, socioeconomic, sexual and behavioral, and legal issues for cancer survivors were reviewed [58]. In 1971, there were 3 million cancer survivors increased to 12 million in 2012 [58]. Over 70% of children cancer survivors survived longer than 10 years [58]. More than 50% of cancer survivors had treatment related side effects [58], many of these are chronic and severe, or life threatening [58]. Cancer survivors also had needs for health maintenance counseling, increased unemployment and workplace discrimination [58].

For children survivors, 2/3 had chronic late side effects from treatment, and 1/3 had severe or life threatening side effects [62]. 62.3% of childhood cancer survivors had chronic condition versus 36.8% for siblings [58,62], 23.8% childhood cancer survivors had 3 or more chronic conditions versus 5.4% for sibling [58,62]. Cumulative incidence of chronic condition is 66.8% at 25 years and 73.4% at 30 years [58,62]. The most common late toxicity after moderate to high dose brain irradiation was poor academic performance [58,62,63]. The most common late side effect for 24 Gy cranial irradiation for central nervous system (CNS) and acute lymphoblastic leukemia (ALL) was educational deficiency more likely to require special education or learning disability programs [64]. In this study, 34 patients treated on average more than 17 years before, 77% scored on the Brief Symptom Inventory (BSI) [65-67], 12% met diagnostic criteria of post-traumatic stress disorder (PTSD) [65,68].

In this study [58], for adults there is an estimated cumulative risk of 10-30% radiation induced cardiac disease occurred 5-10 years from treatment, and 5-15% for radiation pneumonitis [58,69]. Left ventricular ejection fraction (LVEF) is the most widely used measure for cardiac toxicity [70].

According to National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) data, 16% of all cancers are second malignancy due to factors including prior radiation therapy and chemotherapy treatments [58]. For children, a study by Children Cancer Survivor Study included 14358 study members, there were 703 reported 802 secondary cancers, excluding non-melanoma skin cancers [71]. These could be due to host, disease or treatment related factors [71]. Among 18862 5-year survivors of Hodgkin's disease, 30 year cumulative risk of secondary solid malignancy was 18% for men and 26% for women [72]. For small cell lung cancer survivors, there was a 30% risk of secondary cancer for two years or more survivors [73]. In this study, using 2000 National Health Interview Survey for health behavior (diet, exercise and smoking), only 10% of cancer survivors and 9% of non-cancer persons had discussion of all three topics, more counseling is needed on these topics [74].

In this 2014 study, people diagnosed with invasive cancer during 1994 to 2011, were still alive were included [75]. Data were obtained from Ireland National Cancer Registry, included cancer site, sex, current age, marital status, initial treatment, and time since diagnosis [75]. Ireland had a population of 6378000 in 2011 [76]. The 17-year cancer prevalence was 58054 males and 54556 females [75]. The four most prevalent cancers for females were breast (26066), colorectum (6598), melanoma (4593) and uterus (3505) [75], and for males were prostate (23966), colorectum (8207), lymphoma (3236) and melanoma (2774) [75]. 39% female survivors were < 60 years old, 35% > 70 [75], 25% and 46% respectively for males [75]. More than half of patients with bladder, colorectal and prostate cancer were 70 or older [75]. 50% of testis cancer patients were younger than 40, 28% for female leukemia patients and 22% for male leukemia patients, and 20% for cervical cancer patients, 19% lymphoma female patients and 20% for lymphoma male patients [75]. 57% female patients were married, 64% for male patients [75]. 25% female patients had 10 or more years of follow up and 18% for male patients [75]. 69% patients had surgery, 39% had radiotherapy, 32% had chemotherapy and 18% had hormone therapy [75]. Survival for cancer patients has been increasing 1-2% per year, and the 5-year relative survival for all cancer survivors were more than 50% [77]. 3.9% of the population in Ireland were cancer survivors [75].

Short term cancer survivors beyond first year post diagnosis may require more rehabilitation services [75,78], high prevalence of anxiety 2 or more years post diagnosis may require more psychological support [75,79], and 10 years or more long term survivors may require more attention to the late side effects and detection of second cancers [75,79].

This chapter discusses briefly the difficulties cancer survivors face, and their needs for support. Cancer is no longer a uniformly deadly disease, some patients would unfortunately succumb to the disease, for many who survived their journeys to return to live a normal life with their loved ones may still be very difficult. This is a vast and worthwhile topic and will be expanded in future discussions.

A neighborhood train station, Brooklyn.

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Chapter - 4

Adult Palliative Oncology and Radiotherapy of Locally Advanced and Metastatic Cancers

INTRODUCTION

End of life care is perhaps the most challenging in oncology [80-87] but a learnable skill [81]. Hospice care is a top priority of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology, and National Comprehensive Cancer Network (NCCN) [81,88-90]. Palliative care involves compassionate care and meticulous attention to the psychological needs of the patients and their families [81-87]. Radiotherapy is important in palliative care in oncology patients [91]. About 30% of breast cancer patients are diagnosed with stage IV disease [92]. About 50% of breast cancer patients with distant metastasis have radiotherapy as part of their palliative care [93]. Treating patients with advanced and metastatic disease could provide palliation and sometimes may prolong survival [94]. Palliative care is often complex, a multidisciplinary team may be most appropriate [92,95-97].

This paper does not attempt to be comprehensive but attempts to make choices on the best practices in palliative radiotherapy, and will also discuss other palliative modalities. This paper is part of a series [2,3,5,6,27,98-105] discussing current challenges of designing radiation treatment target volumes. This paper includes quite a bit of technical details of radiotherapy and the associated local and systemic treatments because the target volumes needed in radiation treatment are intimately related to the treatment techniques being used, and the other treatments the patients receive.

END OF LIFE AND AGGRESSIVE TREATMENT

Performance status [106] is a useful predictor of length of survival of cancer patients receiving palliative radiotherapy [107-110]. Patients with poor performance status (Karnofsky Performance Status (KPS) < 60), non-breast and non-bone metastasis [107] have a median survival of 13 weeks, patients with two out of these three poor prognostic factors have a median survival of 29 weeks, and patients with good prognosis survived for a median of 114 weeks [107].

Use of radiotherapy during the last 30 days of life, regarded by many as inappropriate, was 7.6% for top five most deadly cancers lung, breast, prostate, colorectal and pancreatic cancers [107,111]. In another study, aggressive chemotherapy during the last month of life increased the chance of emergency room visit and intensive care unit admission for stomach cancer patients [112].

SIMULATION AND SETUP

The goal of simulation is to set up the patient in a way that is comfortable and reproducible especially for palliative cases [113-115]. Cancer pain could be aggravated by the daily radiotherapy process (e.g. simulation, immobilization, transportation) and has been undertreated in about 50% of patients [116-118]. During simulation, the iso-center is set usually at the center of the target volume. However, at the treatment machine, when the simulation film is lined up with the port film for low dose CT using bony landmarks, the isocenter may no longer be at the center of the target volume because the position of the target volume is not representative of the average position of the target volume on daily basis [119] possibly due to discomfort of the patient at simulation. This is called the systemic error in addition to the random error due to internal organ motion secondary to respiratory, bowel or bladder filling [120-123]. When system error is large, re-simulation may be required [114,115,119]. Excessively uncomfortable immobilization, especially in palliative cases, may cause pain and discomfort and cause an excessive systemic error in simulation. No correction level of error (typically a few mm) could be applied so that patients need not be moved daily to adjusted for minor systemic setup errors [124,125].

TREATMENT PLANNING

Familiar with the CT and MRI characteristics of tumors is very useful for treatment planning. CT number is a measure of the tissue density relative to that of water, it could be negative/dark (e.g. air in lung) if the density is lower than that of water [126]. Tumor necrosis is a sign of an aggressive tumor [127]. The tumor necrotic center contains largely fluid appears dark on CT [127]. The CT level is usually chosen as the mid value of the CT numbers, and CT window is the range of CT numbers to display [126]. For high resolution imaging, an entire volume of tissue could be imaged to multi-slice CT that acquires all the slices in one revolution as opposed to acquiring each slice one at a time and reconstructs the volume leading to reconstruction artifacts [126]. See [128] for a very useful online reference for tumor imaging.

For brain tumor imaging [128,129], it is useful to note that fat is dark on CT (- 100 HU), bright on both T1 and T2 MRI [128]. Extra-cranial tumors (about 80% are meningioma and schwannoma) or arise from outside the brain or its coverings, intra-axial tumors are mostly (about 75% are metastasis or astrocytoma) [128]. Extra-cranial tumors do not have blood brain barrier (BBB) so the contrast enhances homogeneously, with a broad dural base and a dural tail of enhancement [128]. The dural tail is not part of meningioma, and needs not to be treated routinely unless there is a radiographic evidence of invasion [130]. Meningioma, glioblastoma multiforme (GBM) and radiation necrosis (appears similar to GBM) could cross the midline, and multiple sclerosis (MS) could present as single or multifocal masses [128]. Radiation brain necrosis shows finger like edema on T2 MRI and heterogeneous gadolinium enhancement on T1 MRI with contrast after the necrosis liquefies [131,132]. Brain tumors, infarction, infection or demyelinating disease (MS) that destroy the BBB, and pituitary and pineal glands that do not have BBB will enhance with

contrast [128]. Pituitary stalk runs at an angle inferiorly to the pituitary gland [128], similar and close to the optic path. The brain tumor and normal tissue interface usually appears differently with different imaging modalities [128,129,133]. The volume of brain tumor imaged by T2/FLAIR could be larger than T1 with contrast MRI [134]. Contrast enhanced CT in the arterial phase clearly delineates the margin of hepatocellular carcinoma [135,136]. Multimodality imaging may be needed for accurate (not under or over covering) target delineation using the composite image [133,134].

Contouring of brain target and normal tissue volumes is best performed in multi-planes. The contouring is not purely anatomical, but also biologic and clinical (considering, for example, the performance status and concurrent chemotherapy). Pre-planning of the treatment volumes (target and normal tissue volumes) is useful.

DOSE AND FRACTIONATION

A protracted course of many weeks may not be the most effective ways for the patients to spend their last few months [113]. A typical hypo-fractionated palliative dose is 3000 cGy in 10 fractions and is highly effective, especially with concnurrent chemotherapy [109,137,138]. In this case report, 30 Gy in 10 fractions was used with nedaplatin (80 mg/m2 (day 1)) and 5-fluorouracil (800 mg/m2 (day 1-4) [138]. The patient continued with chemotherapy and had 17 months of local control of 3.9 x 3.5 cm lower esophageal squamous carcinoma [138]. In this study, 6 Gy once a week for 5 weeks was used to treat a very advanced squamous cell skin cancer with good pain control [113]. Other dose fractionation could very from 8 Gy x 1 for a simple bone metastasis, to 4 Gy x 5 fractions for different sites, 8.5 Gy x 2 fractions for lung cancer, and 2 Gy x 23 fractions for many sites [91,109]. Very high dose per fraction has high risk of radiation side effects, for example, 8 Gy x 1 has more risk requiring re-treatment [139], and injury from the re-irradiation and pathologic fracture [91]. Periosteal edema could happen in about 40% of patients with bone metastases receiving 8 Gy x 1 radiotherapy requiring more analgesic use [140,141]. This could be rescued by 8 mg dexamethasone for 1 to a few days [140-142]. 1700 cGy in two fractions over 3 days provided about 70% relief from hematuria and about 50% relief from pain [143]. The older hypo-fractionated high dose regimens should be used for patient with very limited life expectancy less than one year [91,143,144].

PAIN CONTROL

Pain control is a very important but sometimes ineffective area in palliative care [145]. In South Korea, it is estimated about 60% of cancer patients experience cancer pain, 90% of cancer pain is controllable, however, cancer pain is undertreated in about 40% of patients [145]. This under-treatment is related to oncologist's poor knowledge of using opioids and alternative pain control methods, exaggerated fear of opioid addition and fear of respiratory suppression [145,146]. World Health Organization (WHO) has published a widely used pain control ladder for pain control in patients with advanced cancers [147,148].

Neuropathic pain includes somatic pain that is sharp (e.g. from cutting) versus visceral pain (e.g. from distention and ischemia) that dull and arching [149]. Radiotherapy and analgesic are important components in cancer pain control [150,151]. Mild pain could be treated with non-steroidal anti-inflammatory drug (NSAID) and paracetamol [150,152], moderate pain could be treated with mild narcotic (e.g. codeine, tramadol, dextropropoxyphene) [150] and severe pain could be treated with morphines [150]. Neuropathic pain could also be treated with anticonvulsant gabapentin and tricyclic anti-depressants [150] and steroid [153].

BONE METASTASIS

For patients with spinal metastasis, radiotherapy is a standard of care treatment, it provides about partial pain relief in about 60% and complete pain relief in about 30% patients [91]. Patients with spinal metastasis could also be treated with vertebroplasty and kyphoplasty [91]. Bone cortex and marrow have no nerve endings [150,151]. Neuropathic [154] bone pain from metastatic disease could be caused by fracture, irritation of periosteum and endosteum, nerve root compression and muscle spasm [150]. Treatment of bone metastases related event is about US $28000 and treatment coats about US $10000 per patient [150,155]. Bone fracture is the most common event related to lytic bone metastasis [155]. CT long bone cortical involvement of more than 30% should be considered for prophylactic fixation prior to radiotherapy [156]. Zoledronic acid was the first bisphosphonate used to treat bone metastasis and strengthen the bones [150]. Bisphosphonates such as Aredia could relieve malignant bone pain in 50% of patients [150,157]. Bisphosphonate inhibits osteoclast activity and could impair bone integrity and bone healing [158]. Bisphosphonate related mandible (maxilla less commonly) necrosis could be confused with metastatic disease that include PET avidity, tissue sclerosis and stranding [158].

LUNG CANCER

For patients with large lung cancers, radiotherapy is largely palliative [159]. When the tumor is larger than 7 cm, chemotherapy (four courses in 3-week intervals: intravenous carboplatin with area under curve of 5 [159,160] on day 1, oral vinorelbin 0 mg/m2 days 1 and 8) and radiotherapy (hypo-fractionated 42 Gy/ 15 fractions) improved overall survival from 9.7 months to 13.4 months compared with chemotherapy alone [159]. The patients received chemotherapy first and needed radiotherapy were treated with 17 Gy over 2 fractions [159].

About a third of lung cancer patients have hypercalcemia especially patients with squamous cell lung cancer [155]. Hydration, diuretics (40 mg furosemide IV every 12 to 24 hours), glucocorticoid (60 prednisone orally daily or 100 mg hydrocortisone IV every 6 hours), IV bisphosphonate normalize malignant hypercalcemia in most patients [155]. Bronchial obstruction could be relieved by endoscopic cryotherapy [161] and radiotherapy.

TRIPLE NEGATIVE BREAST CANCER

For triple negative (ER (estrogen receptor) negative, PR (progesterone receptor) negative, Her2 (human epidermal receptor) negative), estrogen receptor alpha targeted therapy has been used to treat patients with triple negative metastatic breast cancer [162]. One of its major side

effects is cachexia secondary to loss of nutrient sensing and metabolism leading to muscle wasting and fatigue [162].

STOMACH CANCER

In one study, 30 Gy in 3 Gy fractions provided about 70% relief from blood transfusion from gastric bleeding for more than a month [137], about 50% of the patients developed rebleeding [137]. The median time to rebleeding in the study was 3.3 months [137], and patients received concurrent chemotherapy had lower rebleeding rate [137]. Bleeding from stomach melanoma been treated with more hypofractionated 16 Gy in 4 Gy fractions that provided 4 months of relief, and could be retreated with 9 Gy in 3 Gy fractions in this case report [163] . In this study, a median dose of 35 Gy in 14 fractions to the stomach provided control for bleeding, dysphagia/obstruction and pain in about 70-85% of patients [164], and control for the remaining part of life in about 50% of these patients [164]. A biological equivalent dose (BED) of equal or more than 41 Gy was found to be needed for good control of gastric symptoms [164].

COLORECTAL CANCER

For colorectal cancer patients, obstruction and perforation is usually managed by colonic resection, stoma, lavage, internal bypass or stenting [97]. Bleeding, pain or tenesmus and fullness could be managed by radiotherapy [97].

Brain and brainstem metastasis Radiotherapy Oncology Group (RTOG) performed a trial comparing whole 5 x 4 Gy versus 15 x 3 Gy or 20 x 2 Gy, the survival was the same using the shorter or the longer courses of radiotherapy [108]. The risk of neurotoxicity was higher with the large dose pre fraction whole brain radiotherapy [108]. Brain stem metastasis is challenging to treat because it is located in the critical area [165-167], brain stem metastasis less than 1 ml may be safely and effectively treated with Gamma Knife stereotactic radiosurgery with a median dose of about 16 – 18 Gy prescribed to 50% [165-167]. For larger brain stem metastases or patient received whole brain radiotherapy, they could be treated with 21 – 30 Gy in 3 -5 fractions [166]. In this study, MRI T1 with gadolinium contrast was used to define the target, no clinical margin was used [166]. Six months survival after Gamma Knife SRS (minimum of 16 Gy) was 42%, with shorter survival for patients also received whole brain radiotherapy (3750 cGy whole brain followed by 16 Gy or less SRS boost) in this study [167]. Neurocognitive function is worse after whole brain and SRS when compared with SRS [168]. Upfront SRS for solitary or limited brainstem metastasis may be the better treatment saving the whole brain radiotherapy for salvage [167] in palliative cases.

CONCLUSION

The radiotherapy in palliative cases is different than the curative cases in the intent of cure versus palliation. When active intervention is futile, palliating the pain and suffering of the cancer patient should be the primary treatment goal.

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Chapter - 5

Target Volumes, Image Fusion and Contouring in Modern Radiotherapy Treatment Planning

INTRODUCTION

In modern radiotherapy using ultra-tight treatment margins to spare normal tissues, accurate target delineation is very important. Traditional 2-Dimensional (2D) simulators we used for decades [169] are now replaced by computed tomography (CT) and magnetic resonance imaging (MRI) [170]. Modern radiotherapy relies on 3D imaging data [171] that require contouring of the gross target volume (GTV), clinical target volume (CTV) and planning target volume (PTV). GTV includes the tumor imaged and all other pertinent information, CTV includes clinical at risk area of microscopic spread and lymph nodes at risk, internal target volume (ITV) includes CTVs from different respirator phases, and PTV includes the set up errors [169]. This paper is part of a series [2,3,5-7,172] discussing some of the challenges and solutions of modern radiotherapy planning. For specific cancer sites, this study primarily focused on important aspects related to treatment planning of head and neck, and breast cancers as specific cancer sties.

OBSERVER VARIABILITY IN TARGETING AND CONTOURING

There are well-known inter-observer and intra-observer variations for contouring of target [173-176] and normal tissues [177,178]. For example, in one study, the median PTV and the ratio of the largest to smallest contoured volume were respectively 9.22 cm3 (range, 7.17 –14.3 cm3) and 1.99 for pituitary adenoma [175], and 6.86 cm3 (range 6.05 – 14.6 cm3) and 2.41 for meningioma. Some plans used 1-2 mm PTV margin, some used 0 mm margin is this study [175]. When the contours superimposed onto the "ideal" plan, there is an excessive dose of 23.64 Gy (up to 268% of the default plan) in pituitary adenoma and 24.84 Gy (131% of the default plan) in meningioma to the optic nerve [175]. The optic tract dose was to kept within 50 Gy (in equivalent dose of 2 Gy fractions). Overall, contouring variability and errors are the most important challenge to modern 3D and 4D radiotherapy treatment planning [176].

IMAGE FUSION AND CONTOURING VARIABILITY BECAUSE OF IMAGING MODALITIES

Understanding the strengths and limitations of various imaging modalities is important in modern radiotherapy treatment planning. PET/CT has been found to be very useful in contouring

of GTVs in treatment planning. When a dedicated PET-CT is used, the target volume could be directly contoured on the PET-CT [179]. Otherwise the PET-CT needs to be fused to the treatment CT, by registering the CT of the PET-CT to the treatment CT in most cases [179]. The information from the registration is used to bring PET of the PET-CT to fuse with the treatment CT [179]. It has been found that using the 40-50% standardized uptake value (SUV) is the best in contouring based on phantom [180] and 20 – 40% in some clinical studies [181]. Part of the PET SUV blurring comes from respiratory motion [181]. In one study [182], 50% PET value and CT lung window and level of 1600 and -300 Hounsfield Units (HU) when the cancer is in the lung correlated best the pathologic size of the cancer. Mediastinal window and level of 600 HU and 40 HU were used when the tumor was close to the mediastinum [182]. The contouring on the fused PET image could facilitate contouring on the CT and MRI that are more commonly used imaging modalities in modern radiotherapy treatment planning [170,182,183]. Cone beam CT used for on-board imaging has poor tissue contrast making it more difficult to contour especially for pelvic tissues [184,185]. MRI (3D and 2D) data can better imaging the pelvic tissues [170,186-188] but would require more complex imaging during radiotherapy.

CONSENSUS AND CHALLENGES IN TARGET AND NORMAL TISSUE CONTOURING

The Radiation Therapy Oncology Group (RTOG) [176,189,190] and other US and international radiotherapy groups [176,191,192] have developed site specific contouring atlases since around 2009, when Intensity Modulated Radiotherapy (IMRT) and 3-Dimensional Radiotherapy (3D-CRT) became the standard of care Blood vessels were found to be a good surrogate for lymph nodes and CTVs [193]. Contouring in 3D radiotherapy era is very time consuming, for example, the average time in contouring an oropharyngeal cancer case was about two hours [194]. It may be even more time consuming when 4D CT scan data are used [195]. Auto-contouring and semi-automatic programs have recently been developed to save the clinician time in contouring [196-201], including some specialize on using RTOG consensus atlases [202]. However, these auto-contouring programs still need to be validated before clinical use. Other than time consuming, 3D target and normal tissue contouring remain to have many challenges as discussed in this paper.

HEAD AND NECK TARGETING AND CONTOURING

The IMRT for head and neck cancer is relative new, only about 10 years [169]. It produced equivalent clinical outcome compared to the large amount of clinical data accumulated in the 2D era [169], but with less toxicity mostly better salivary function [169]. Usually, elective head and neck radiation treatment is used when the nodal recurrence is about 15-20% [169,194].

The RTOG guidelines for head and neck contouring are limited to N0 disease. In this study [194], the contouring variability of a node positive (N+) head and neck patient was studied. It was found that, the target to treat in oropharynx has shown significant variability even for published head and neck IMRT experts [194]. Some investigators have chosen to treat ipsilateral neck only

for advanced stage III tonsillar cancers [194], the doses were variable ranging from 66 Gy to 70 Gy in 2 Gy fractions [194]. In this study [194], 8 out of 20 academic and community centers used one level of CTV dose level, twelve used two CTV dose levels (high-risk and low-risk CTVs). Five of these twelve centers used an expansion of GTV and used the same dose level as used for the GTV [194]. The mean target volume irradiated was 250 cc (range 37 – 676 cc) [194]. All centers covered the levels II and III, 95% covered the retropharyngeal lymph nodes and 85% covered the ipsilateral level Ib nodes [194]. Average CTV to PTV expansion was 4.11 mm (0 – 15 mm) [194]. The average time clinicians contouring the target and at risk organs was about two and a half hours [194]. Some clinicians use concurrent chemotherapy [194], but significant number of centers did not. Thus treatment variability remains a challenge even for a typical oropharyngeal cancer. Most of the information on normal tissue tolerance has been collected with 3D conformal radiotherapy [203-205]. Only, recently head and neck normal tissue tolerance in the IMRT era has been published [206]. More normal tissue tolerance information is needed in the IMRT era.

BREAST CANCER TARGETING AND CONTOURING

Breast cancer surgery has become more conservative over the past few decades moving away from radical mastectomy [169]. Recently more breast cancer patients undergo immediate breast reconstruction that could present a challenge to post-mastectomy radiotherapy [207,208]. Breast reconstruction using tissue expanders is associated with capsular contraction and other complications after radiotherapy [209,210], autologous more vascularized transplant is more appropriate when radiotherapy is planned [211]. Irradiated flap could atrophize about 21% while 16% in non-irradiated refs over 6-10 months [211]. In a randomized trial RESTORE-2, tissue defect up to 150 mL are eligible for the surgical reconstruction [211]. Recently, DIEP (deep inferior epigastric perforator) flap has been used in additional to TRAM (transverse rectus abdominis myocutaneous flap) [211-213]. In one study, a higher rate of complication was observed in the minority of patients who received 10 Gy scar boost [214]. However, overall post mastectomy radiotherapy (PMRT) to the usual dose of about 50-50.4 Gy in 1.8-2 Gy fractions can be safely used after immediate or delayed breast reconstruction [209-214]. For reconstructed breast lumpectomy cavity, and with surgical clips placed, the lumpectomy cavity is contoured as the GTV and CTV is the same as the GTV [215] as compared with traditional lumpectomy cavity contouring when seroma is contoured as a GTV, and GTV to CTV of about 1 cm is typically used [215]. MRI can better see the lumpectomy cavity because of the fluid intensity on T2 MRI [216].

In modern era, the side effects of post-operative breast cancer radiotherapy include cardiac toxicity, arm lymphedema, pneumonitis, neuropathy, skin changes [217]. Trastuzumab is associated with cardiac toxicity (1-4%), unlike anthracyclin-related cardiomyopathy, it is not dose dependent, rarely causes death, and reversible when treated or when the drug is discontinued [217]. Trastuzumab is not used concurrently with anthracyclin because of cardiac toxicity [217]. Breast cancer radiotherapy after 1990 using modern techniques showed similar advantages for left sided versus right sided breast cancer patients [169,217].

Pericarditis and related pericardial effusion have decreased from 20% to 2.5% using modern 3D techniques [217]. Local regional radiotherapy is related to 4.1% of radiation pneumonitis, and 0.9% for local radiotherapy [217], 3.9% when treated with chemotherapy and 1.4% without chemotherapy [217]. Using supraclavicular and axillary fields has a 9-58% of arm lymphedema, the rate is negligible when these fields are not used [217]. Skin thickening and fibrosis occur in 1/3 of patients and in 5% for severe fibrosis [217]. Arm lymphedema occur in 13% of patients after lymph node dissection versus 1-3% using sentinel lymph node dissection [217]. Thus sparing the cardiac and other normal tissues, by following the recommended organ at risk (OAR) guidelines, has become an important area of investigation over the past 2-3 decades and remains to be very important [205].

For hypofractionated whole breast radiotherapy, 40 Gy in 2.67 Gy fractions is usually used, 9 Gy in 3 fractions is used to boost the tumor bed [218]. In one study [218], patient is immobilized by a wing board and other personalized immobilization device [218]. CTV includes the whole breast tissue, and is expanded 5 mm to get the PTV [218]. Heart and lungs are contoured as OARs [218]. The median breast volume was 760.64 cc (range 44.77 –1892.1 cc) [218]. The median boost volume was 143.33 cc (23.07 – 230.02 cc) [218]. Median time to first skin reaction was 12 days (5 – 40 days) [218]. Other dose fractionations have also been used in whole breast hypofractionated radiotherapy and have similar outcome and cosmesis when compared with standard fractionation [218,219]. American Society of Radiation Oncology (ASTRO) recommended patients older than 50 years old, T1-T2N0, without chemotherapy, and dose homogeneity less than <7% are appropriate for hypofractionated whole breast radiotherapy [218]. The use of boost was associated with acute and late skin toxicities [218].

CONCLUSION

Over the last couple of decades, much has been learned about targeting the correct treatment volumes, the use of multi-modal image fusion to aid contouring and using advanced simulation (e.g. 4D), and image guided radiotherapy. However, as discussed about, this will be a continuous process along the progress in radiotherapy.

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Chapter - 6

Modern Topics on Stomach Cancer Radiotherapy

INTRODUCTION

In modern radiotherapy of high-precision radiotherapy of stereotactic radiotherapy (SRT), intensity modulated radiotherapy (IMRT), and image guided radiotherapy (IGRT), target delineation is very important [1,6,20,27,99-101,104,169,220,221]. To date, traditional 2D (2-dimensional) simulator we used only twenty years ago has largely been replaced by computed tomography (CT) and magnetic resonance imaging (MRI) [170]. Modern radiotherapy relies on 3D (3-dimensional) imaging data [171] that require contouring of the gross target volume (GTV), clinical target volume (CTV), internal target volume (ITV) and planning target volume (PTV) [169]. Gross target volume includes the tumor imaged and detected by clinical examination [169,222]. Clinical target volume (CTV) includes clinical target volume at risk of microscopic spread including the lymph nodes at risk [169,222].

Planning target volume includes the organ motion and set up errors [172,223]. This paper is part of a series of papers on contemporary challenges facing radiation oncology [1,6,20,27,99-101,104,221]. This short review is not intended to be exhaustive, the author hopes the selection of topics would be useful to readers. As in previous papers [1,6,20,27,99-101,104,221], this papers goes into details of established standards as these may be useful in guiding actual treatments in the clinic.

Stomach cancer is the fourth leading cause of cancer globally with an expected incidence [42,43] of about 1 million in 2002, and an estimated 700000 died from the disease in 2002 [224-226]. Stomach cancers [227] are mostly adenocarcinoma (90%) of the stomach [169,228], and the remaining 10% include lymphoma [229-231] and gastrointestinal stromal tumor [169,228].

GASTRIC CARCINOGENESIS

Gastric carcinogenesis could involve the traditional linear step by step metaplasia (mostly occur in the intestinal type) induced by various carcinogens, but it also may involve a large step mutation (mostly occur in the diffuse type) from normal gastric histology [228].

Proliferative index (Pi [232]) is an important prognostic factor for stomach cancer [233]. Histologically, there are three gastric mucosa types (cardia, fundus/corpus, antrum/pylorus)

and transition zones joining these zones [228]. Anatomically, pylorus has two parts pyloric antrum and pyloric canal that ends with pyloric sphincter opening into the duodenum [228,234]. Intestinal type gastric adenocarcinoma metastasizes orderly by the portal venous system to the liver, while the diffuse type has high propensity to spread diffusely, into the peritoneum and has worse outcome [228].

SURGICAL TREATMENT

Gastroesophageal junction carcinoma has been classified by Sievert and Stein in type I distal esophageal cancer, type II real cardial cancer and type III subcardial cancer [235]. Distal gastric adenocarcinoma is associated with Helicobacter Pylori [236] infection. Early stomach cancer has about 90% cure rate with surgical resection as occur in South Korea and Japan where stomach cancer surveillance is common [226,237,238]. Early stomach cancer is defined as mucosal gastric cancer or submucosal gastric cancer with our without lymph node metastasis [237,238]. In Western countries, most stomach cancers are diagnosed at an advanced stage with tumor invasion into or through the muscular wall, and/or involving the perigastric lymph nodes [226]. 30% of these patients are curable with surgery alone [226]. About 80% of patients with advanced gastric cancer will die within on one year [228].

The standard of care recommendation is D1 resection with at least 15 lymph nodes removed [239]. Modified D2 lymph node dissection excluding the distal pancreatectomy and splenectomy and patients with T3/T4 disease might improve local regional control with minimum added toxicity compared with less than D2 lymphadenectomy [240,241]. D2 resection has been proposed as a standard of care [240,241].

ADJUVANT TREATMENT

Eleven single modality adjuvant chemotherapy have not been successful so far [226,242,243]. But important efforts are continuing to improve the outcome [244-246]. Two randomized trials INT-0116, and MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) has demonstrated overall survival advantage of adjuvant treatment after curative surgery [224].

In this pivotal U.S. study published in 2001, combined chemoradiotherapy was found to improve survival [247]. 556 patients with 1988 AJCC (American Joint Committee on Cancer) stage IB to IV M0 patients, with R0 resection [239] were included [247]. Only patients with adequate organ functions were allowed into the study: creatinine concentration not more than 25% above the normal limit, normal hemogram, bilirubin concentration not more than 50% above the normal limit, serum aspartate aminotransferase concentration not more than 5 times of normal limit, alkaline phosphatase concentration not more than 5 times of normal limit, caloric intake of 1500 kcal [248] per day or more [247].

In the INT-0116 trial, fluorouracil (5FU, 425 mg/m2/day) and leucovorin (20 mg/m2/day) was given on day 1 to 5, followed by chemotherapy (attenuated dose when administered with

radiotherapy) and radiotherapy on day 28, one month after completion two 5-days cycles of chemotherapy were given one month apart [247]. Radiotherapy to the tumor bed, regional lymph nodes (those covered in a D2 resection [245]), and 2 cm beyond the proximal and distal margins was given to 4500 cGy in 180 cGy fractions [172,247,249]. For GE (gastroesophageal) junction tumor, paraesophageal and paracardial lymph nodes were included but not the pancreatoduodenal lymph nodes [247,250]. Hemidiaphragm is covered in proximal tumors [245]. In this study, the median survival of the surgery group was 27 months, 36 months in the adjuvant group [247].

In the INT-0116 trial, one percent patients died from toxicity, grade 3 toxicity occurred in 41%, grade 4 in 32% of the chemoradiation group [247]. 17% of patients did not finish the adjuvant chemoradiation because of toxicity in the INT-0116 trial [245]. Some centers have replaced bolus 5FU by infusional 5FU as commonly used in other gastrointestinal tumors, and some centers are using ECF (epirubicin, cisplatin, 5FU) before and after the radiotherapy [245].

Current fields used are more limited than that of INT 0116 to avoid excessive toxicity [244,245]. Many perioperative chemotherapy and radiotherapy regimens are being tested in randomized trials [240,244].

ORAL CHEMOTHERAPY

Capecitabine is an oral fluoropyrimidine which is a less toxic but as effective as continuous 5FU infusion [239]. In this study, 1250 mg/m2 twice daily on days 1-14, followed by one week break, followed by concurrent chemoradiation with twice daily 825 mg capecitabine without weekend break [239]. After two weeks break from the end of radiotherapy, 3 cycles of 1250 mg/m2 twice daily on days 1-14 were given [239]. In this study, the CTV included the tumor bed, duodenum stump, remnant stomach, anastomosis, regional lymph nodes, and extended 2.5 cm beyond the resection margins [239]. The radiation dose was prescribed according to the International Commission of Radiation Units (ICRU) [239]. 77% patients completed the treatment, 96% of patients reached the radiation dose of 45 Gy [239]. No toxicity related death occurred [239]. 8.9% had grade 3 or 4 hand-foot syndrome, 18.8% had grade 3 or 4 infection [239]. Intensive nutrition support was given [239]. 58.4% patients lost weight with median weight loss of 5 kg (1-17 kg) [239]. The 4-year overall survival was 66.2% [239].

PATTERN OF CARE IN US

There are wide variation of treatment for gastric cancer [251]. In this 2013 Quality Research in Radiation Oncology (QRRO) study, clinical performance measures (CPM) were added to the pattern of care study (PCS) [251]. The CPMs (1. use of CT based simulation, 2. use of dose-volume histogram that was first extensively used in prostate cancer radiotherapy [252], and 3. finishing RT within 33-45 days) are used to provide feedback to the clinicians about adopting evidence based radiotherapy use [251]. This study used two tier cluster sampling to randomly select these institutions from 1879 U.S. radiation facilities [43,253]. In this study of treatment performed

in 2005-2007 [251], 45 institutions were included, 99.5% patients had CT based radiotherapy treatment planning, 75% used DVHs (dose volume histogram) to evaluate doses to kidneys and liver, 70% 0f patients completed radiotherapy in the 33-45 days time frame, IMRT was used for 22% patients, and IGRT was used for 17% patients. IGRT included PET, MRI, respiratory gating and 4DCT [251].

NORMAL TISSUE CONTOURING

The Radiation Therapy Oncology Group (RTOG) [176,189,190] and other US and international radiotherapy groups [176,191,192] have developed site specific contouring atlases since around 2009, when Intensity Modulated Radiotherapy (IMRT) and 3-Dimensional Radiotherapy (3D-CRT) became the standard of care in the past two decades.

In this 2014 study, RTOG organized a consensus panel to develop the correct contouring for upper abdominal organs in preparation for a relatively novel irradiation site hepatocellular carcinoma for RTOG 1112 sorafenib [254] versus SBRT followed by sorafenib trial [255]. A panel of experts who have published or participated in trials of upper abdominal sites and one specialty radiologist were included [254]. Contouring this region has many challenges including variant anatomy, terminology not usually used in radiotherapy [255]. In this study, the patient was scanned with 64 slice CT scanner, in supine position, during a breath hold, 100 mL of intravenous contrast and 1000 mL of water were used, 3 mm slices with 1.5 mm interslice interval were obtained in the portal venous phase [254]. Most of the experts contoured six normal organs esophagus, GE junction, liver, common bile duct, stomach and duodenum [254]. A S95 (95% confidence interval for true and consistent contouring) was developed for these six organs [254]. The rest of the 39 structures were also contoured [254].

Coronal view is critical in accurate contouring of the duodenum which begins from pylorus and ends with ligament of Trietz [254]. For the liver contour, inferior vena cava and gallbladder should be excluded [254]. Oral contrast may be needed for accurate small bowel contouring [254]. In this RTOG study [254], difficult organs to contour was found to be the segment I of liver, GE junction, common bile duct, and 4th part of duodenum. None of the experts completed common bile duct contouring [254]. Complete contouring of the duodenum has been recommended by the RTOG experts, however complete duodenum contouring has not been performed consistent performed so far and thus the dose volume constraints for duodenum are derived from partial duodenum contouring [254].

2D VERSUS 3D RADIOTHERAPY

In this study from 2014, it compared the dosimetric difference between using conventional 2D versus CT based 2D planning in treating stomach cancer postoperatively [256]. This study included patients with high-risk T3-T4 adenocarcinoma of the GE junction and stomach and/or node positive patients [256,257]. In this study, the 2D plan was based on pre-operative CT which

was used until July of 2009 [256], and the 3D plan was based on CT simulation at the Samsung Medical Center [256]. 321 patients with gastric cancer after curative resection and D2 lymph node dissection from 2006-2008 were included [256]. The conventional and CT based 2D plans of 158 patients were included [256]. The patients treated with CT based 3 fields were excluded.

The patients were matched for stage (stage IB – IV) in the study [256]. 43.3% of the patients had Billroth I subgastrectomy (with direct remnant stomach to duodenum anastomosis [258]), 13.3% had Billoth II subgastrectomy (with remnant stomach to jejunum anastomosis [259]), and 41.7% had total gastrectomy [256]. For the conventional 2D radiotherapy, the patients were simulated supine, arms down, oral contrast was used to identify the stomach remnant, anastomotic site, and duodenum remnants [256]. The upper border extended from the top of T11 to bottom of L2 to include the head of pancreas in the study [256]. Right lateral border was placed at the most lateral margin of the porta hepatis before the bifurcation of the portal vein, or the duodenum remnant or the pancreatic head with a 1-cm margin [256]. Left lateral margin was placed one vertebral body away from the spine [256]. For CT based 2D treatment, the field borders were placed similarly to the 2D treatment but individualized based on anatomy [256]. For the CT based treatment, the remnant stomach was not included, the anatomatic site was not included when there was a 5 cm of tumor free margin [256]. The regional lymphatic of stomach cancer follows the major arteries [172]. In this study, the CT based APPA (opposed anterior and posterior fields) was found to have better dosimetry but not better tumor control or toxicity outcome with a median follow up of 28 months [256]. These results may be particularly useful for clinics in regions that are still using conventional 2D radiotherapy techniques [256].

CONCLUSION

This paper summarizes the important topics relevant to contemporary radiotherapy of stomach cancer, it will provide a basis for future discussion and papers.

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Chapter - 7

Modern Topics on Pancreas Cancer: Etiology, Epidemiology, Public Health, Treatment and Cancer Genomics

INTRODUCTION

There were 1,456,496 invasive cancers reported in U.S. in 2010 except Arkansas and Minnesota [260]. By state in 2010, the all cancer incidence rates ranged from 380.4 to 510.7 per 100,000 [260]. Cancer incidence rates per 100,000 were 503 for men, 405 for women, and 455 for African Americans (highest by race and ethnicity) [260]. The most common cancer for men in U.S. was prostate cancer (126.1 in 100,000), lung and colorectal cancers, and for women was breast cancer (118.7 in 100,000), lung and colorectal cancers [260]. Behavior related health risks smoking, obesity, lack of physical activity, and human papilloma virus (HPV) infection were related to the risk of developing cancer [260].

Pancreas cancer is a highly lethal disease globally [261]. In 2001, estimated number of new pancreas adenocarcinoma cases was 22,050 for men and 21,980 for women, estimated number of deaths was 19,360 for men and 18,300 for women [262,263]. In 2012, pancreas cancer caused 330,000 deaths globally [262,263]. Pancreas cancer was the fifth most common cause of cancer death in Europe with more than 104,000 deaths (6% of all cancer deaths) in 2012 [264,265]. This paper uses the terms pancreas cancer, pancreatic ductal adenocarcinoma, pancreatic adenocarcinoma and exocrine pancreas cancer interchangeably [261,263,264,266,267]. The 1-year survival for pancreas cancer is about 18% and the overall 5-year survival is about 4% [264]. The progression from pre-malignant pancreatic intraepithelial neoplasias (PanINs) to invasive pancreas cancer takes about 17 years and to death in another 2-3 years [264]. This paper is a part of a series of ongoing discussion on challenges facing global oncology, epidemiology [20,172,268,269] and public health [1,104] as well as treatment using advanced radiation treatment machines [1,27,99-101,104,270]. This paper also discusses the rapidly emerging field of cancer genomics [1,104] as related to pancreas cancer. This paper discusses in some details and attempts to quantify the effects of various factors on pancreas cancer causation, treatment outcome and public health. This paper does not attempt to be exhaustive, hopefully topics chosen here are useful to the readers.

ETIOLOGY

The etiology of pancreas cancer is grouped into four major categories [271]. In this study, the relationship between mortality and smoking was prospectively assessed by using questionnaires from 1951 to 1991, 34,439 British male doctors were included [272]. Half of the mortality was found to be related to smoking [272]. Pancreas cancer was three times more common in heavy cigarette smokers than non-smokers [272].

In this study, 2015 individuals from six countries with a diagnosis of chronic pancreatitis were included [273]. In the study, the diagnosis of chronic pancreatitis was made on a combination of factors of chronic epigastric pain and steatorrhea, presence of pancreatic calcification, evidence of pancreatitis on ultrasound, endoscopic retrograde cholangiopancreatography [274], computed tomography, results of secretin-pancreozymin or secretin-cerulein test, fecal fat test, or fecal chymotrypsin assay [273]. Of the 29 patients with suspected pancreatic cancer two or more years after diagnosis of pancreatitis, the diagnosis of pancreatic cancer was made in 24 patients by surgery or autopsy, 5 by exploratory laparotomy, and 3 by clinical course, laboratory and radiographic studies [273]. The pancreatitis was alcoholic for 77%, idiopathic for 17%, hereditary in 1.9%, and 4.1% for all other reasons [273]. 63% of the patients consumed 100 g of alcohol per day or more (one drink is defined as 10-15 grams of ethanol [275,276]), 71% smoked one pack of cigarettes or more, 64% had pancreatic calcification, 47% had diabetes, 7% had cirrhosis and 46% underwent surgery for chronic pancreatitis [273]. After a mean follow up of 7.4 years, the expected number, adjusted for age, sex, and center, was 1.76 [273]. In this study, the risk ratio of pancreatitis for age 40 to 59 years of age was 3.1 (95% confidence interval 1.1 to 8.6), and for 60 years or older was 9.7 (95% confidence interval 2.7 to 35.1) when compared with subjects less than 40 years old [273], no other risk factors were significantly associated with pancreas cancer in this study [273]. There was no difference between alcoholic versus non-alcoholic pancreatitis and the risk of pancreas cancer [273].

In this study, 20 out of 30 screened case-control and cohort studies [42] published from 1975 to 1994 were pooled [277]. Inclusion criteria included duration of diabetes for at least one year, and before diagnosis of pancreatic cancer. The pooled relative risk (RR [43]) of pancreatic cancer for diabetic to non-diabetic patients was 2.1 (95% confidence: 1.6 to 2.8) [277].

In this study carried out from 1984 to 1988 in The Netherlands, in collaboration with the International Agency for Research on Cancer [278,279], 176 cases of exocrine pancreatic cancer and 487 controls were included [279]. There was an inverse relationship between allergy-related conditions and the risk of pancreatic cancer (odds ratio 0.57, 95% confidence interval: 0.36 to 0.96). In this study, history of pancreatitis was not related to the risk of pancreatic cancer [279]. In men, insulin dependent diabetes diagnosed more than one year has an odds ratio of 11.66 (95% confidence interval: 1.28 to 105.95) in developing pancreas cancer [279]. Stool frequency less than once a day relative to once a day had an odds ratio of 2.10 (95% confidence interval: 1.09 to 4.04) [279].

CANCER GENOMIC

Pancreas cancer has a large number of mutations, and most mutations occur in a small number of patients [264], making it necessary for individualized cancer genomic study to assess risk and design treatment strategies [1,104]. Only CXCR4 has been linked to rapid progression and metastasis of pancreas cancer [280]. The major mutations found so far in pancreas cancer KRAS [281], P16 [282], P53 [283] and Smad4 [284] have no effective inhibitors available [264].

Hereditary pancreatitis is a autosomal dominant disease with about 80% penetrance [285,286]. In this study, there was a 40% lifetime risk of pancreatic cancer associated with hereditary pancreatitis [285]. Hereditary pancreatitis is due to serine protease 1 or cationic trypsinogen [287] gene (PRSS1) gain of function mutations [288] on chromosome 7q35 [285]. Since 1996, there are 30 mutations found in PRSS1 [286]. In this study [285], 37 physicians from 10 countries contributed medical records of 218 patients thought to have hereditary pancreatitis as the most likely diagnosis [285]. Inclusion criteria included early onset 30 years or younger, positive family history, and no other causes that could be related to pancreatitis [285]. PRSS1 mutations were mainly found in Caucasian patients [288].

Cationic trypsinogen gene mutation was however not found in a study included 11 Korean patients with chronic idiopathic pancreatitis [288,289]. In this study, the patient was a 55 years old woman with 3 month history of recurrent abdominal pain, jaundice and steatorrhea [288]. She shortly later died from pancreatic cancer [288]. However, 2 symptomatic and 6 asymptomatic members of her immediate family were included in the study, both individuals with chronic pancreatitis had PRSS1 mutations [288]. It may be important to screen young patients with recurrent abdominal pain and hyperamylasemia [285].

EPIDEMIOLOGY AND PUBLIC HEALTH

Pancreas cancer is rare in developing countries [271]. The northeast Nile Delta region is the most polluted area in Egypt [271], it covers 150 mile of coastline and 99 miles in length [290]. There is a high incidence of early onset pancreas cancer in the Nile Delta region [271]. In this study, 31 newly diagnosed pancreatic cancer patients and 52 hospital control subjects were included [271]. The odds ratio (OR) for cadmium [269] was 1.12 for serum cadmium level and 3.25 for farming for developing pancreas cancer [271].

In the Mississippi Delta, there is very high level heavy metal pollution in soil and water because of increased industrial activities in the southeast of America [291,292]. In this study, the serum cadmium level did not vary with rural versus urban residence or smoking status [271]. There was a trend towards significance with occupation with farmers showed the highest level with a mean of 13.34 ng/mL [271]. The odds ratio for cadmium was 1.12 and 3.25 for farming [271]. In this study, 5 men were followed for 10 to 13 years, it was estimated that the cadmium was eliminated from the body with a half-time of 75 to 128 days for the initial clearance and a half-time of 7.4 to 16.0 years from the whole body [293].

In this study, 5,886 chemical manufacturing workers were included [294]. 28 pancreatic cancer cases and 112 matched controls were included [294]. The risk ratio for ever exposed to organic pesticide DDT [295] to never exposed was 4.8 (95% confidence interval: 1.3 to 17.6) for developing pancreas cancer. When the mean exposure was 47 months, the risk ratio was 7.4 times [294]. Exposure to DDT derivative Ethylan and DDD were associated with risk ratio of 5.0 and 4.3 respectively [294].

Water chlorination started around 1905 [296]. Chlorine is a strong oxidizing agent that could oxidize organic compounds found in the drinking water [296]. This water disinfectant byproduct is called trihalomethane (THM) [296]. Bromoform and dibromochloromethane are the two main forms of THMs [296]. Humic acids are organic acids that are the final decomposition product of dead plants and animals [297]. Cleaning up water, air and soil pollution is important for public health and cancer prevention [1,104,270].

The age adjusted death in U.S. in 2011 was 740.6 per 100,000 persons [298]. Death from cancer was the second leading cause [298]. A person born in 1900 had an average life span of 47 years, in 2010, 76 years for men and 81 years for women from birth [298,299]. It is worth noting that a man at 65 years old is expected to live another 17.8 years (more than the average life span estimated at birth), a woman at 65 years old is expected to live another 20.4 years [299]. Associated with aging is an increase genomic instability that is also related to carcinogenesis such as pancreas cancer [273,299]. Aging is also associated with commonly condoned prejudice and a sense of loss [299,300]. These factors are important in caring for the aging cancer patients [299,301]. Aging is associated with preventable cancer risk factors that could be modified such as decreasing obesity, alcohol consumption and cigarette smoking [273,299], especially starting at midlife 45–64 years old [299]. Non-invasive screening for pancreas cancer for high risk individuals are being studied [263].

In 2014, the first meeting on integrating genomic information into public health studies gathered experts in genomics, public health, medicine, law and bioethics in Rome to discuss the use of genomic data in public health [302]. As in this study, it has been found that eating fried food increases rate of obesity for individuals who are genetically predisposed to obesity [303]. It may have implications for public health intervention in reducing obesity.

SURGICAL TREATMENT OF PANCREATIC CANCER

Pancreaticoduodenectomy (Whipple procedure [304]) is the best chance of cure for resectable pancreatic head cancer [305]. About 20% pancreatic cancer patients have a resectable disease (celiac artery and superior mesenteric artery are free of tumor invasion or abutment) [261]. It is recommended to refer to NCCN (National Comprehensive Cancer Network) guidelines for resectability [306]. R0 resection is possible for patients with duodenal, portal or superior mesenteric vein involvement [306]. Consensus has been reached definitive biopsy is not required for a head of pancreas mass before surgery [305]. The chance of having benign lesion is 5-13% [305]. Pancreatic operation is complex [307-309]. There is a learning curve [308,310]. In this study,

there were 60 pancreasticoduodenectomy operations performed over 5 years, the outcome improved for the second 30 of the 60 operations [310]. The residents always performed the biliary and gastrointestinal anastomosis, and sometimes pancreaticojejunostomy reconstruction [310]. Most of the complications from pancreas cancer surgery come from pancreaticojejunostomy related fistula, abscess and hemorrhage [311,312]. In this study, the percent of patients received adjuvant therapy increased from 58% to 91% with learning [310], this indicated better patient recovery and good pre-surgery treatment planning [310]. In this study, the outcome of first 60 cases versus the second 60 cases as an attending of pancreaticoduodenectomy were compared [307], the median blood loss was 1100 mL versus 725 mL, length of stay 15 days versus 13 days, and operative time was 589 minutes versus 513 minutes [307], positive or suspicious margins were decreased from 30% to 8% [307].

In this SEER (Surveillance, Epidemiology and End Results)-Medicare study, One out of five patients after pancreaticoduodenectomy were re-admitted within 30 days in U.S. [313]. Surgical complications have important implications for post surgery health and employment status of the patients [314]. Function outcome of surgery is important in assessing the quality of surgical treatment [315]. To assess the quality of treatment, cost alone should not be the judging criteria, death may be the worst complication and outcome of treatment and yet may be associated with lowest cost [315].

CHEMOTHERAPY OF PANCREAS CANCER

In this 2007 German/Austria study, 6 months of gemcitabine chemotherapy improved the median disease free survival from 6.9 months to 13.4 months [316]. Both R0 (negative margin) and R1 (positive margin) subgroups benefitted [316]. There was no difference in median overall survival, 22.1 months for gemcitabine group and 20.2 months for control group [316]. In this 2009 paper, pooled ESPAC (European Study Group for Pancreas Cancer) trials data showed that adjuvant 5-FU [317] and folinic acid decreased the risk of death by 30% [318]. In this 2011 French study, four drug FOLFIRIRNOX (folinic acid, fluorouracil, irinotecan and oxaliplatin [319]) regimen improved median overall survival from 6.8 months to 11.1 months when compared with single drug gemcitabine regimen [320].

The discussion of end of life palliative care is complicated and important for aggressive disease such as pancreas cancer [301]. The most important goal of for end of life care should be providing a gentle and supportive environment and to allow the patients be surrounded by love and caring [301]. Pain control is important for patients with advanced pancreas cancer [321]. Oral route morphine for pain control is preferred [316].

RADIOTHERAPY OF PANCREATIC CANCER

Intensity modulated radiotherapy (IMRT [322]) is a type of advanced 3D radiotherapy that was used for head and neck cancers to spare the salivary function [323]. IMRT requires contouring of target and organ at risk volumes using the computer images from simulation. In this study, the risk of lymph node metastasis to various cervical lymph node levels were studies

for nasopharyngeal carcinoma [324]. To precisely contour all the lymph node stations require knowledge of the lymphatic drainage on CT [324]. Contouring is done best in 3D [98,172]. To ensure appropriate coverage that is supported by the data from the decades of 2D radiotherapy it is advisable for new practitioners of 3D radiotherapy and IMRT to compare the 3D fields with the 2D fields [1]. In this study, for example, it put corresponding 2D fields to the 3D fields [1,325,326] to make sure the structures were covered.

The traditional dose to pancreas cancer is 5040 cGy in 180 cGy fractions or 3000 cGy in 10 fractions [169,327], involved field treatment is preferred with chemoradiation [169]. Even with 50 Gy in conventional fractionations, the risk of ulceration, perforation and late stenosis if the patient survive long enough is substantial [327].

HYPOFRACTIONATED RADIOTHERAPY OF PANCREAS CANCER

Inoperable non-small cell lung cancer (NSCLC) SBRT (stereotactic body radiotherapy [1,104]) provides important lessons in extracranial hypofractionated radiotherapy SBRT of other sites including pancreas cancer [327-329]. SBRT developed from stereotactic radiosurgery (SRS) [327]. SBRT requires advanced tumor imaging, patient immobilization, tumor tracking (such as using Cyberknife Synchrony tracking the intrafraction motion [1,104]), gating (the linear accelerator is on only when the target is in the range), and motion suppression [327]. RTOG 0236 was the first North American cooperative group trial using SBRT for NSCLC [328]. Inoperable patients with tumor less than 5 cm were included [328]. PET value of 2 or less mostly represented atelectasis [328], and was not included in NSCLC SBRT treatment planning [328]. The SBRT dose was delivered over a range of intervals (60 Gy over 3 fractions, minimum separation of 40 hours and maximum of 8 days, i.e. 3 fractions over 1 1/2 week or 2 weeks total) [328]. No additional margin was used to account for microscopic extension [328]. The 60 Gy was found to be an overestimation after RTOG used inhomogeneity correction in the dose calculation [328]. The dose was close to 54 Gy in 3 fractions [328]. The target expansion was 5 mm axial, 10 mm craniocaudal, when the target moves more than the expansion margin [328], breathing control was used [328]. Image guidance confirming the target position for each session was required [328]. These treatment planning lessons could be used in SBRT planning of pancreas cancer. The control rate was twice the conventional results and severe toxicity was uncommon because no central tumors were included in this study [328]. It is unclear if it is related to improved targeting using advanced radiation treatment machine or from the biological advantage of SBRT.

In this study, pancreas cancer 7.5 cm or less were treated with SBRT 25 Gy in one fraction, equivalent to 74 Gy in 1.8 Gy fractions [330]. 3-5 fiducials were implanted [330], CT simulation was performed 7-14 days afterwards to allow for seed migration [330]. Advanced immobilization using custom made foam forming mattress alpha cradle was used for each patient [330]. Beginning 2004, 4D CT and PET imaging were incorporated into the treatment planning [330]. Biphasic CTs were co-registered with the end respiration 4D CT using the fiducials as the registration points accounting for organ deformation occurred during the scans [330], additional 2-3 mm was used for PTV expansion to account for set up error [330].

For IMRT followed by SBRT, the regional lymph nodes, peripancreatic, celiac, superior mesenteric, periaortic and porta hepatis were treated to 45 Gy in 1.8 Gy fractions with 5-FU chemotherapy [330] followed by a boost of 25 Gy in one fraction [331]. In this study, IMRT in addition to SBRT of pancreas cancer did not improve survival when compared with SBRT alone and had more toxicity [331]. Similarly in anther cancer site, adding EBRT to SBRT for prostate cancer also increased toxicity but not cancer control in this study [332]. The SBRT was delivered with Cyberknife with synchrony for respiratory tracking [330]. The study included duodenum, other bowels, spinal cord, liver, stomach as organs at risk to calculate the normal tissue constraints [330]. The tolerance limit used for duodenum was 22.5 Gy < 5%, and 50% isodose line should not reach the duodenal wall on the other side of the lumen [330]. In the Cyberknife synchrony system only the fiducials implanted in the target were tracked and the beams were adjusted almost continuously during the treatment [330]. Note that the position of the normal organs were not tracked [1].

SBRT for pancreas cancer may be more biologically effective, is convenient to the patient, and allow the systemic treatment to continue [330]. Single fraction dose higher than 20 Gy may significantly increase the apotosis of endothelial cells causing tumor ablation [333]. Gemcitabine could be restarted 2 weeks after the SBRT [327,330]. Fiducials have the size of a grain of rice [334]. More than one fraction SBRT has also been used for pancreas cancer [261,332]. More studies are needed to quantify the biological advantage of SBRT because of hypofractionation versus improved targeting using advanced radiotherapy machines [1,104].

SBRT has been found to be a safe and effective treatment for re-irradiating pancreas cancer [335].

POSTOPERATIVE RADIOTHERAPY OF PANCREAS CANCER

Radiotherapy is indicated for positive margin after surgical resection [327,331]. Post-operative local recurrence map has been studied for radiotherapy field design [336]. For post-operative treatment whether SBRT is standard of care is still controversial [336]. Pre-operative pancreas cancer volume was incorporated into the treatment field design in this study [336].

4D RADIOTHERAPY OF PANCREAS CANCER

In this study, using data from Cyberknife fiducial based treatment of pancreas cancer, the superior inferior (SI) range of motion of the pancreas centroid could move up to 4.5 mm - 48.8 mm (mean 20.8 mm), left right (LR) up to 1.5 mm to 41.3 mm (mean 11.3 mm), and anterior posterior (AP) up to 1.6 mm to 68.1 mm (mean 13.4 mm) [337]. For the 4D CT simulation maximum inspiration and expiration scans, the range of motion of pancreas centroid was SI 0.9 mm to 28.8 mm, LR 0.1 mm to 13.7 mm, and AP 0.2 mm to 7.6 mm [337]. Thus 4D CT may not be sufficient to estimate the margin required for SBRT of pancreas cancer.

In another fiducial based study in 2010, the relative movement of pancreas to bone was AP 0.2 (0.1 -0.5 cm), SI 0.5 (0.2- 1.5 cm) and LR was 0.4 cm (0.2 to 0.9 cm) [338]. These differences were

calculated from the differences in alignment using bony landmarks versus by fiducials [338]. Care should be taken when the radiation treatment system use the bony landmarks for image registration during alignment such as Cyberknife spine tracking when the target has excessive relative movement to the bony landmarks as illustrated by these measurements.

In this treatment planning study in 2014 [339], free breathing, normal inhale breath hold and normal exhale breath hold scans were used (as a substitute for 4D CT). SBRT was delivered during free breathing [339]. Free breathing CT scans were blurred and tissue density averaged by respiratory motion [339]. In the study, PTV using GTV plus 1.5 cm expansion to allow for SBRT using skeletal alignment, and PTV as ITV plus 3 mm (to account for intrafraction target motion), the GTV plus 1.5 cm approach was not able to meet the normal tissue contraints [339]. Using bony alignment and the 3mm margin, the target coverage was found to be inadequate [339]. Because of poor tissue contrast for abdominal organs using CBCT, the authors recommended intratumoral fiducials with tight margins for abdominal tumor SBRT [339].

PET IMAGING AND CA19-9

In this study, 165 pancreatic cancer patients (median age of 67 years old) were included [340]. These patients received surgery, SBRT, conventional radiotherapy or chemotherapy as treatments [340]. SUV max of PET (F18 positron emission tomography) of flourodeoxyglucose (FDG) uptake was classified as low when it was lower than 4.1 and high if 4.1 or higher [340]. The half life for F18 is about 10 minutes, injection of the radioactive tracer needs to be performed shortly before the imaging [340]. It is most useful in nodal and metastatic staging [340]. The higher PET value has worse outcome [340].

Survival was higher for patients with low CA (carbohydrate antigen) 19-9 [341] that is an antibody binds to Sialyl-Lewis X (a cell surface homing carbohydrate important for metastasis) [342].

PET/CT is a hardware solution to improve PET and CT fusion [343]. However there could be motion during the time lapsed between the two scans making the fusion imperfect [343]. This should be kept in mind when using the fused PET/CT for treatment planning [343].

CONCLUSION

Pancreas cancer is an aggressive disease that is challenging to treat. It is a significant source of morbidity, mortality and suffering. Many of the risk factors of pancreas cancer are modifiable. Eliminating or modifying these risk factors may decrease the burden of pancreas cancer, and prevent premature deaths.

Epilogue: Verse and Reverse of Medicine and Arts

A quiet multi-ethnic intersection, Brooklyn.

To know a place or a culture, I would make a friend, to know the community health, I like to walk and take quiet notes about my neighborhoods. I now live in Brooklyn where Bishop lived and wrote about how the sea broke at its shore [344], into foams of creamy dreams. On a summer's day, Brooklyn's bay is as warm as the limpid Gulf, a beauty along the 23 degrees north parallel, that would be appreciated even by a winter's snow man transported into the summer (Wallace Stevens [345]). We usually find new knowledge at the edge if we care and pay attention. Public health studies the neglected, a modern quantitative discipline studying Steinback's underbelly. Yates, an intellectually unjealous and honest man, once said to help a place, write beautiful things about the place, I would agree, I like to write about my neighborhoods and the best of us. I also like to take pictures symbolic post-scripting the neighborhoods, where tiers of meanings concentrate and multiply. Sometimes I would pick a nice neighborhood to photograph and let the meaning unfold with time. I verse and reverse some of my lines and writings based on how my friends

and neighbors react to my works, and sometimes their views are as diverse as all of us, some are more acute and vocal than most, and are always helpful. I use computer to read, listen and analyze writing including dense prose and poetry. Below is a analysis of the sounds (WavePad, NCH) of the second line of Shakespeare's sonnet 18 [346]. I like poetry because of it has its peculiar accents, spellings and even grammar. Subtle suggestions and body language of immigrants from different cultures may require different keys to decode [347-350]. Words and their accents in the rackets of the street like drama at street corners could signal different meanings depending on the frame of mind and culture. Beware of the Yate's challenge [351] of twists and turns, never just settle for the surface meanings. Second line of Shakespeare's sonnet 18 [346], capital letters are accented:

As I pointed out before, social media could be used as a modern way to keep personal and community files, to post and take from the social media, and once the community forms it will take on a life of its own, a seemingly unstoppable force for goodness when used appropriately. We all seem to live in two worlds, one with social media incessant messaging, sometimes it is hard to say which one is more real, but the one is lucking barely right under the surface of the other [50]. However, in the computer age, our computer is known to be able to monitor our health [352] and possibly improve it. Finding quality, multi-ethnic, multi-tiered, timely solutions and the courage to solve public health problems could save lives [353].

Brooklyn is a beautiful multi-ethnic community where there are large immigrant Asian and Hispanic populations, and Eastern and Central European populations. There are language barriers, difference in cultural influences they have to overcome [56,349,354-358]. Their unbearable longings for their homeland could be hauntingly deep, their memories condensed into lines on their faces for the years passed and passing. On a Sunday morning, to pick a path, a ship, a tabernacle on high sea, tentatively diverged in the rising sun, overnight dews rolled down lily petals before they disappeared into the heat of the sun [344]. Old and young fishermen at a nearby seashore fishing, to watch the tidal waves, along a rail into the cherry red sky. Enjoying hardy dragon eyes on a simple plastic plate. Spending a day there could shake loose creases of any weary face. It must be one of the most beautiful places along 42 degrees north parallel.

In the end, immigrants here like everywhere else in our immigration history [359] will integrate into their beautiful new community that will cater for their needs, mend their tender hearts, and some of them will become our new pillars who will support our society. Any cross road is difficult to navigate. Our patients deserve the best. I like to write about the best all of us, to bridge the gulf between suffering and happiness for them. @Brooklyn 9.9.2015.

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