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والصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
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UNIVERSITÉ CADI AYYAD

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Radiation-Induced Secondary Malignancies: The Experiences of the Avicenne Military Hospital, Marrakech

THESIS

PRESENTED AND DEFENDED PUBLICLY ON 13/06/2023

BY

Ms. Dorcas Tobi OKESHOLA

Born on 30th June 1995 in Yaba (Nigeria)

TO OBTAIN A MEDICAL DOCTORATE

KEYWORDS

Cancer – Radiotherapy– Secondary Malignancies – Risk Factors – Prevention– Treatment

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بسم الله الرحمن الرحيم
قَالُوا سُبْحَانَكَ لَا
عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا ط إِنَّكَ
أَنْتَ الْعَلِيمُ
الْحَكِيمُ
سورة البقرة- الآية 32
صدق الله العظيم

HIPPOCRATIC OATH

At the time of being admitted as a member of the medical profession:
I solemnly pledge to dedicate my life to the service of humanity;
the health and well-being of my patient will be my first consideration;
I will respect the autonomy and dignity of my patient;
I will maintain the utmost respect for human life;
I will not permit considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient;
I will respect the secrets that are confided in me, even after the patient has died;
I will practice my profession with conscience and dignity and in accordance with good medical practices;
I will foster the honor and noble traditions of the medical profession;
I will give to my teachers, colleagues, and students the respect and gratitude that is their due
I will share my medical knowledge for the benefit of the patient and the advancement of healthcare;
I will attend to my health, well-being, and abilities in order to provide care of the highest standard;
I will not use my medical knowledge to violate human rights and civil liberties, even under threat;
I make these promises solemnly, freely and upon my honor.

Declaration of Geneva, 1948

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57	OUALI IDRISSI Mariem	P.E.S	Radiologie
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59	BENJILALI Laila	P.E.S	Médecine interne
60	NARJIS Youssef	P.E.S	Chirurgie générale
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63	EL ANSARI Nawal	P.E.S	Endocrinologie et maladies métaboliques
64	ABOU EL HASSAN Taoufik	P.E.S	Anésthésie-réanimation
65	SAMLANI Zouhour	P.E.S	Gastro-entérologie

66	LAGHMARI Mehdi	P.E.S	Neurochirurgie
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68	BENCHAMKHA Yassine	P.E.S	Chirurgie réparatrice et plastique
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72	ABKARI Imad	P.E.S	Traumato-orthopédie
73	EL BOUIHI Mohamed	P.E.S	Stomatologie et chirurgie maxillo faciale
74	LAKMICHI Mohamed Amine	P.E.S	Urologie
75	AGHOUTANE El Mouhtadi	P.E.S	Chirurgie pédiatrique
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250	DOULHOUSNE Hassan	Pr Ass	Radiologie
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259	ESSAFTI Meryem	Pr Ass	Anesthésie-réanimation
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266	JEBRANE Ilham	Pr Ass	Pharmacologie
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269	AIT LHAJ El Houssaine	Pr Ass	Ophtalmologie
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LISTE ARRETEE LE 22/06/2023

DEDICATIONS

I dedicate this thesis to…..

To God Almighty,

Whose faithfulness and lovingkindness have been my guiding light throughout this journey. It is by His grace that I am here today, and He alone deserves all the honor and praise!

In loving memory of my dear father, Rashidi Okeshola

As I reflect on my journey and the person I have become, I can't help but think of you and the impact you had on my life. It's been 18 years since you passed away, but your memory and teachings still guide me every day. Your unwavering love and support were a constant source of strength and inspiration, and I'm forever grateful for the time we shared. Your legacy of hard work, resilience, and perseverance have been instrumental in shaping my character. You taught me to never give up on my dreams and to always strive for excellence. These values have become the cornerstone of my life, and I owe it all to you. This dedication is for you, my dear father, with love and eternal gratitude. Your memory inspires me to honor your legacy and make a positive impact in this world. I miss you more than words can express, but I take solace in knowing that your spirit lives on in me and in all those whose lives you touched. I love you Daddy!

To my loving and adorable mother Oluwakemi Okeshola

The nursery poem "Who sat and watched my infant head when sleeping on my cradle bed, and tears of sweet affection shed? My mother." seems to have been written based on your loving and caring spirit for your children. You have stood by me, listened to me, prayed for me, and counseled me. You have shaped my life into what it is today, and have done everything you could to give me the life I have today. I am forever grateful and indebted to you for being a great parent who stood strong and ensured we did not feel Daddy's absence. I will live every day of my life paying you back. I love you Mommy you are the best!

To my dear brother Daniel Bolaji Okeshola

Thank you for being an unwavering source of support and inspiration throughout my life. Your role as a father figure has been nothing short of remarkable, and I am forever grateful for the sacrifices you have made to ensure my success. Your selflessness and dedication to our family have been a constant source of strength, and I could not have made it to this point without your unswerving belief in me. Thank you for being my brother, my friend, and my hero. I am blessed to have you in my life, and I will always cherish the bond we share.

To my dear sister, Blessing Foluke Oluwasesan

Your nurturing spirit and ever-present love have been a constant source of strength and inspiration for me. I am sincerely grateful for your commitment to my well-being and the sacrifices you have made to ensure my success. I am blessed to have you in my life, and I will always cherish the bond we share.

To my best friend and sister Queen Adejoke Okeshola

Your role as my sister, best friend, and confidant has been nothing short of amazing. Thank you for being there through thick and thin, for lending a listening ear, and for offering sage advice. You have been an invaluable ally throughout my life, and I cherish the memories we have shared. Thank you for being my rock, my cheerleader, and my friend. I am blessed to have you in my life, and I will always treasure the bond we share.

To my in-laws Yackson Oluwasesan and Rachael Okeshola

Thank you for being a wonderful addition to our family.

To my niece, Zara oluwatobiloba Okeshola and nephew, Zuriel oluwabiyi Okeshola

You are the light of my life and the reason for all that I do. Watching you grow and learn has been one of the greatest joys of my life, and I am constantly inspired by your curiosity, your innocence, and your love. I dedicate this work to you, my dear ones, as a symbol of my deep love and admiration for you both. Although you may not understand its contents yet, I hope that it will serve as a reminder to always follow your dreams and never stop learning.

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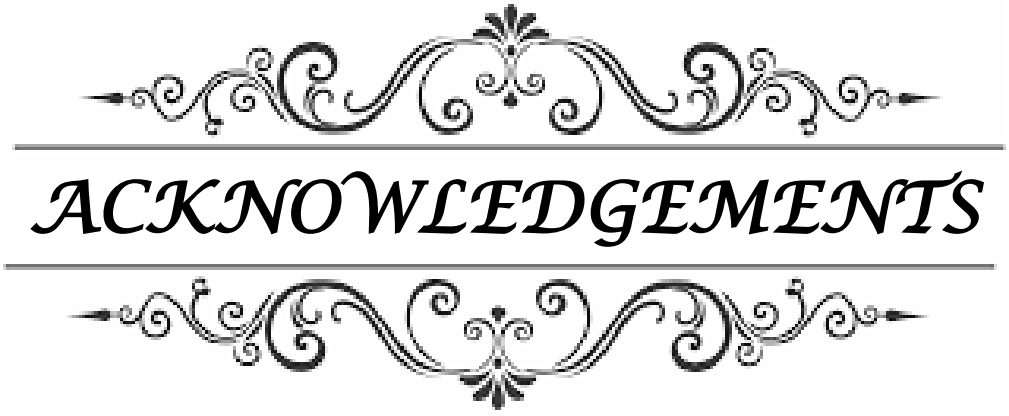

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ABBREVIATIONS

List of abbreviations

BRCA1	: Breast Cancer gene 1
BRCA2	: Breast Cancer gene 2
CHART	: Continuous hyper-fractionation accelerated radiotherapy
CONV-RT	: Conventional radiotherapy
CT	: Computed tomography
CT-TAP	: Computed tomography -Thorax, Abdomen and Pelvis
G-CSF	: Granulocyte-colony stimulating factor
Gy	: Gray
IGRT	: Image-guided radiation therapy
IMRT	: Intensity modulated radiotherapy
LINAC	: Linear accelerator
MLH1	: MutL homolog 1
MSH1	: MutS homolog 1
MSH2	: MutS homolog 2
MRI	: Magnetic resonance imaging
NSCLC-SCC	: Non-small cell lung cancer, squamous cell carcinoma
OGD	: Oesophago-Gastro-Duodenoscopy
OS	: Overall survival
SSC	: Squamous cell carcinoma
PBT	: Proton beam therapy
PMRT	: Post-mastectomy radiotherapy
PMS1	: PMS1Homolog 1, Mismatch repair System component
RAD	: Radiation absorbed dose
Rb	: Retinoblastoma protein
RIOS	: Radiation-induced osteosarcoma
RIS	: Radiation-induced sarcoma
RISMs	: Radiation-induced secondary malignancies
RIOSM	: Radiation-induced osteosarcoma of the mandible and maxilla
ROS	: Reactive oxygen species
RT	: Radiation therapy
SMNs	: Secondary malignant neoplasms
SPECT	: Single photon emission computed tomography
TP53	: Tumor protein 53
US	: Ultrasonography
VMAT	: Volumetric modulated arc therapy
XRT	: Radiotherapy
3DCRT	: 3D-Conformal radiotherapy

FIGURES AND TABLES

List of figures

List of Tables

OUTLINE

INTRODUCTION

Cancer is a disease in which some of the body's cells grow uncontrollably and spread either slowly or rapidly to other parts of the body. This diagnosis was first made in Egypt in the 16th century (1). A survey done in the year 2020 stated that, there are about 18.1 million cases of cancer globally (excluding non-melanoma skin cancer), of which 9.3 million of the people affected were males, 8.8 million females, of these, 2.3 million were new cases and a total of 9.9 million deaths was recorded (2). It is projected that by 2030 the number of cancer cases would have increased to approximately 26 million globally (3). In addition to the conventional anti-cancerous treatments such as chemotherapy, surgery, radiotherapy and hormonotherapy, the therapeutic arsenal was enriched by targeted therapy and immunotherapy.

A German physicist named W. C. Roentgen invented radiotherapy in the 18th century. It was estimated as of 2021 that more than 50% of patients diagnosed with cancer would be treated by radiotherapy (4). Radiation therapy uses high-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells (5). Radiation works by making small breaks in the DNA inside cells (5). These breaks keep cancer cells from growing and dividing, thus causing them to die. Radiotherapy is used alone or in association with other therapies for either curative or palliative purposes.

Radiotherapy has many indications in the management of cancer, notably: -in a curative approach, it is used exclusively, in association with chemotherapy, or preoperatively to reduce tumour mass; in a preventive approach, it is used after surgery to reduce the risk of a recurrence; and in a palliative approach, it is used to relieve or treat the symptoms associated with cancer. All these are achievable through the enhancement of the methods of administering radiation therapy. Among the methods of administering radiation therapy, we have External radiation (or external beam radiation), Internal radiation, and Systemic radiation. The type of method used depends on the kind and location of the cancer.

Although radiation therapy has greatly contributed to the field of oncology, it is believed to be a double-edged weapon as it does not go without some daunting side effects. Some of the general side effects include skin changes, fatigue and second cancer, and other side effects are radiotherapy location dependent. These include dry mouth, mouth and gum sores, hair loss,

nausea, lymphedema, tooth decay, difficulty swallowing, shortness of breath, loss of appetite, diarrhoea, rectal bleeding, bladder incontinence, sexual problems, fertility problems…

Radiation-induced secondary malignancies are very rare and long-term complications of radiotherapy that need to be actively screened for due to the increased life expectancy of cancer survivors. This phenomenon is defined as the development of secondary cancer after the use of radiotherapy in treating primary cancer. Secondary cancers are new entities completely different from primary cancers; it is necessary to note that secondary cancers can affect the same organ but have different histological origins or another organ entirely. Some examples of radiation-induced secondary malignancies are leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, squamous cell carcinoma, bone cancer, central nervous system malignancy, or kidney cancer. In this study, we are going to be looking at three different cases of radiation-induced secondary malignancies, as listed below: I) Chondrosarcoma of the scapula after radiotherapy for lung cancer; ii) Radiation-induced squamous cell carcinoma of the tongue after Hodgkin's disease treatment; iii) Osteosarcoma of the upper thigh after radiotherapy for prostate cancer. With the existence of this grave complication we are left with the following questions;

1. Is there a correlation between the dose administered and the incidence of radiation-induced secondary malignancies?
2. Does the technique used in radiotherapy play a role in the occurrence of a secondary malignancy?
3. Do our patient's environmental and genetic predispositions contribute to developing a secondary malignancy?
4. Does concomitant chemo-radiation increase the incidence of radiation-induced secondary malignancies?

Our study aims to sensitize the medical body to the existence of secondary malignancies after radiation therapy, elaborate on some of the factors that play major roles in this occurrence, and treatment management.

MATERIALS AND METHODS

I. General study description

This is a retrospective descriptive study of radiation-induced secondary malignancies based on the experiences of the Avicenne Military Hospital, Marrakech.

II. Duration explored

We included all patients diagnosed with radiation-induced secondary malignancies since the inception of the Avicenne Military Hospital oncology department in 2013 up until 2022.

III. Population studied

We conducted a study over a 9-year period on patients who underwent radiotherapy treatment at the oncology department of the Avicenne military hospital in Marrakech. Our study relied on the analysis of medical records, including clinical observations, laboratory results, CT-scans, MRIs, scintigraphy, SPECT, and surgical biopsy with histopathological examination and immunohistochemical stain findings. Specifically, we focused on cancer patients who developed a secondary malignancy after radiotherapy treatment.

1. Inclusion criteria

Patients who underwent radiotherapy and later on developed a histologically proven second cancer.

- The tumor should be located in the irradiation field while taking into account the concepts of "threshold dose" and "dose-effect relationship."
- The second tumor's histology had to differ from the first lesions, or if it is a carcinomatous tumor, it had to rule out a metastatic tumor, a second location, a

recurrence, or an evolutionary continuation. In this situation, the deciding factor would be the amount of time between the two cancers and their various locations.

- The appearance time should be longer than three years, with no upper duration limit (radiation-induced tumors can occur more than 30 years after the end of irradiation).

2. Exclusion criteria

Patients who did not undergo radiotherapy, or whose primary cancer metastasized and is/not histologically proven.

RESULTS

Below, we compiled the clinical observations, laboratory tests, and imaging results of our patients before and after the development of secondary malignancies.

I. Patient A

1. Description

A 62-year-old Moroccan man, retired from the army, married with five children, with a medical history of chronic tobacco smoking but non-alcoholic and right lung stage IIIB non-small cell lung cancer, squamous cell carcinoma subtype (NSCLC-SCC) treated by concomitant chemo-radiation in 2007.

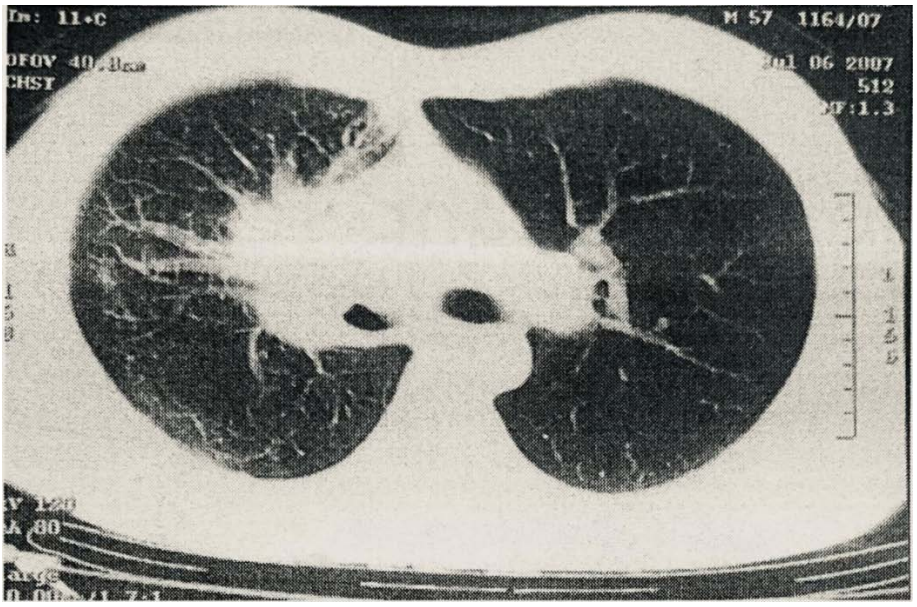

Figure 1: Scannographic axial cut showing a stage IIIB mediastinopulmonary process

2. Adopted protocol

This protocol included radiotherapy using gamma photons of 1.25Mv energy, administered at a total dose of 60 Gy, 2 Gy by fraction during weekdays for 6 weeks, with two

opposing fields including the right scapula. In conjunction with radiotherapy, chemotherapy was used according to the Vinorelbine-cisplatin regimen; Vinorelbine 25 mg/m² day 1 and 8; cisplatin 75 mg/m² day 1, repeated every 3 weeks until the end of radiation therapy. Three cycles was delivered in total.

3. Duration of treatment

Treatment lasted a total of 6 weeks for radiotherapy and 6 weeks for chemotherapy.

4. Progress of patient

After chemo-radiation, the patient was in good health, his regular check-ups did not reveal any pathological findings and with this, he needed no supplementary medication. It is important to note that the patient stopped smoking tobacco in 2007. Unfortunately, 10 years later he presented a right scapula pain, which lasted for 3 months before his admission and was later diagnosed as chondrosarcoma.

5. Clinical findings, procedures and tests after secondary malignancy

5.1. Clinical presentation

On admission, patient was conscious and stable on both respiratory and hemodynamic state, temperature 37.5°C, pulse 90 beats per minute and blood pressure 135/75 mmHg.

5.2. General examination

Upon examination, we found around the right scapula a fixed and sensitive mass, which measured 10 cm on its big axis (Figure 2). Neurologic examination registers a conscious patient, well oriented in time and space with preserved memory. Cranial nerve examination registers preserved function in both the olfactory and visual fields. Ocular motricity as well as facial

sensation and motricity are well conserved. There was no record of dysarthria, hearing loss, and tongue or neck weaknesses in the examination of the other cranial nerves. There were no involuntary movements as the arms and inferior limbs motricity were well conserved. Muscular sensitivity (light touch, temperature, vibration, joint position sense) and force were preserved. It is important to note that he suffered neuropathic pain in his right arm of 4/10 intensity according to the visual analogue scale. No abnormalities were observed in the biceps, triceps, brachioradialis, knee (patellar), and ankle (Achilles) reflexes.

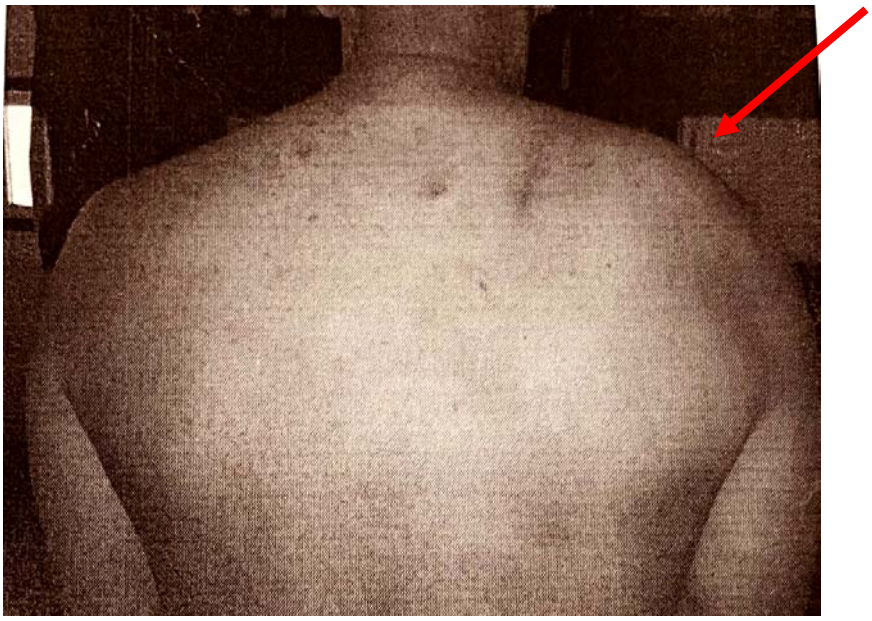

Figure 2: Right scapula mass

5.3. Laboratory tests

This revealed a good liver and renal function without any other abnormalities.

5.4. Imaging

A chest-CT scan showed a tumor process on his right scapula, with sequela lung injury in the territory of the first tumor (Figure 3). Magnetic resonance imaging (MRI) of the scapula region showed a malignant tumor process with hyposignal at T1 and heterogeneous hypersignal at T2 centered on the supraspinous and infraspinous muscles without involving his right scapula

joint, measuring 90 mm on the longest axis and 60 mm on the shortest axis (Figure 4). The data collected from bone scintigraphy was in favor of hyperfixation focused on the right scapula (Figure 5). A single photon emission computed tomography (SPECT) examination showed an osteocondensing and lytic aspect in the spine of his right scapula (Figure 6).

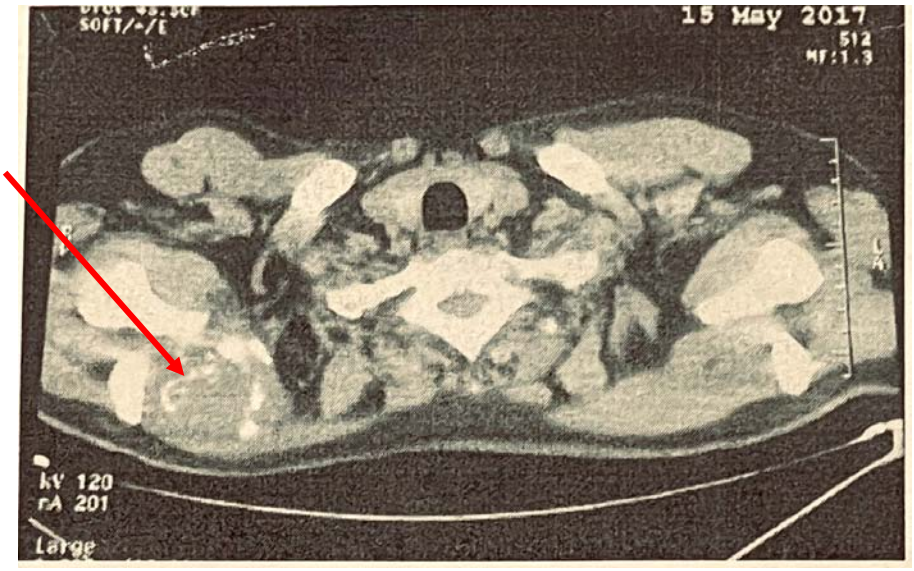

Figure 3: Chest computed tomography axial cut scan showing a tumor process on the right scapula

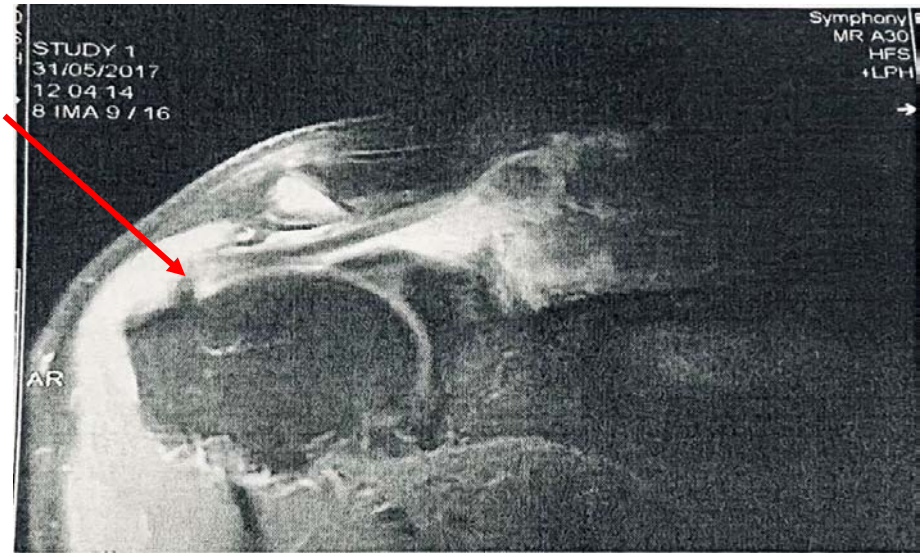

Figure 4: Coronal cut of a Magnetic resonance imaging of the scapula region with malignant tumor process centered on the supraspinous and infraspinous muscles

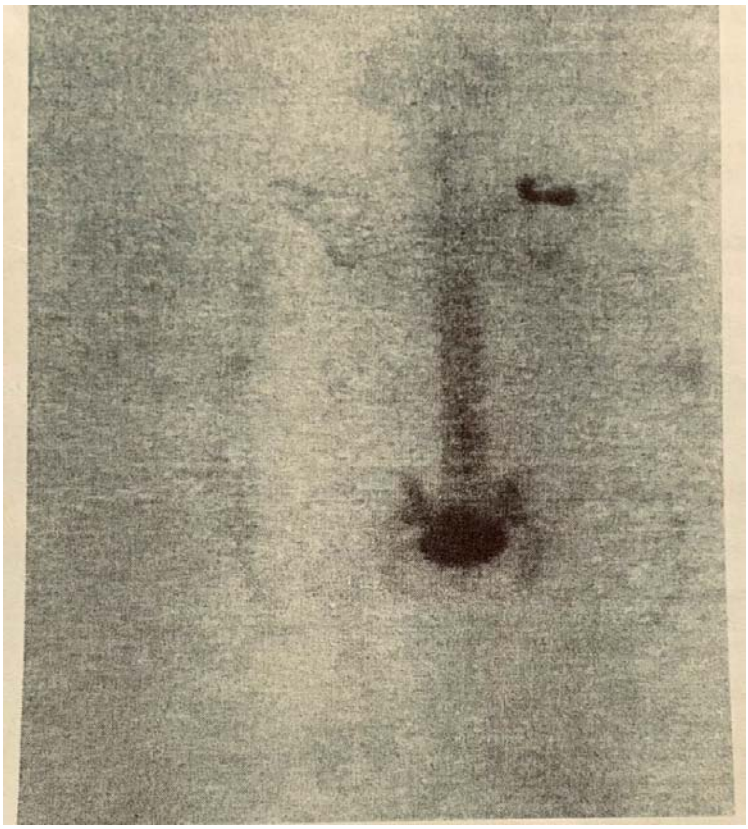

Figure 5: Bone scintigraphy with hyperfixation focused on the right scapula

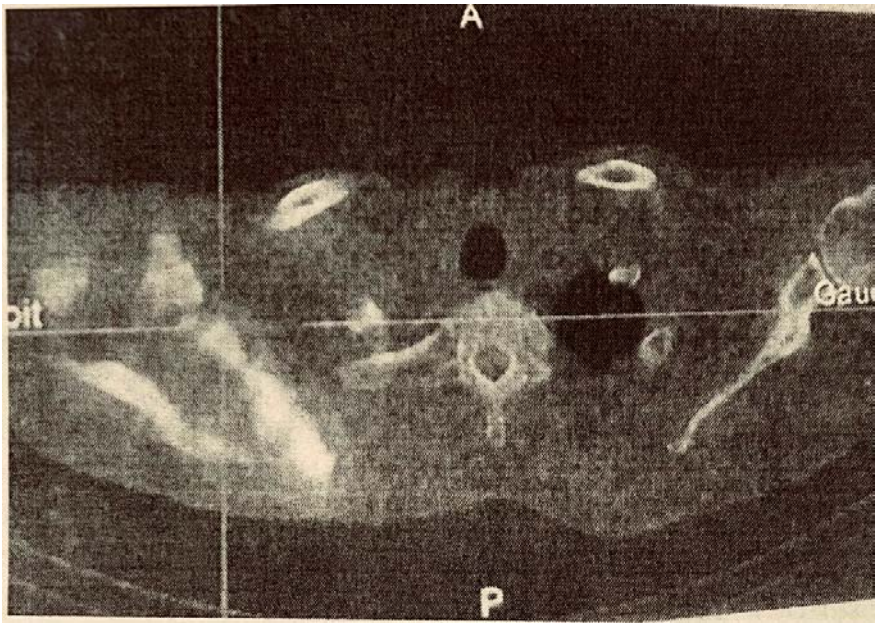

Figure 6: Single-photon emission computed tomography-computed tomography with osteocondensing and lytic aspect in the spine of the right scapula

5.5. Intervention

A surgical biopsy of the tumor was performed and a histopathological examination showed a grade 1 chondrosarcoma (Figure 7).

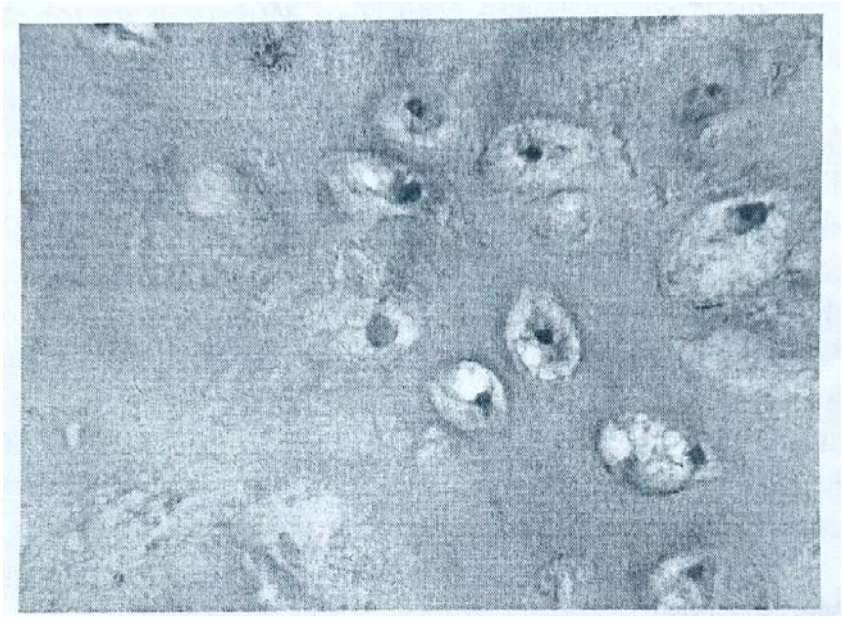

Figure 7: Histopathological examination of the biopsy in favor of grade 1 chondrosarcoma

5.6. Extension assessment

This was done by a chest-CT and abdominal ultrasonography both of which came back clean with no distant metastasis.

Afterwards, a multidisciplinary staff meeting was held to decide on the treatment options.

5.7. Treatment

The tumor was surgically resected with safe margins. This procedure entailed the resection of his right scapula, and thanks to osteosynthesis, the fixation of his right arm was possible. He needed no adjuvant treatment after surgery because margins were free and chondrosarcoma from the histopathological examination was of low grade.

6. Progress of the patient after secondary malignancy

There was no sign of reoccurrence or specific complication during a follow-up done at 6 months post-surgery.

II. Patient B

1. Description

A 65-year-old Arabic male whose medical history is marked by a stage II primary Hodgkin's lymphoma of Waldeiyer's ring treated by concomitant chemo-radiation 14 years prior.

2. Adopted protocol

This protocol involved 4 months of chemotherapy according to the ABVD regimen (Doxorubicin 25mg/m², Bleomycin 10 mg/m², Vinblastine 6 mg/m², Dacarbazine 375 mg/m² day 1 and day 15), followed by radiotherapy using gamma photons of 1, 25Mv energy, delivered by a Cobalt 60 machine, at a total dose of 36 Gy, 2 Gy by fraction, in four weeks, with two opposing fields including the base of the tongue.

3. Duration of treatment

Four months of chemotherapy and four weeks of radiation therapy.

4. Progress of patient

We observed a successful evolution after concomitant chemo-radiation. Unfortunately, 14 years later, the patient presented ulceration and swelling of the right side edge of the tongue base, which happened to be squamous cell carcinoma.

5. Clinical findings, procedures and tests after secondary malignancy

5.1. Clinical presentation

On admission patient presented with ulceration and swelling of the right side edge of the tongue base.

5.2. Imaging

An MRI of the oral cavity showed a mass of 1.5 cm diameter on the right edge of the tongue base with extension to adjacent structures (Figure 8).

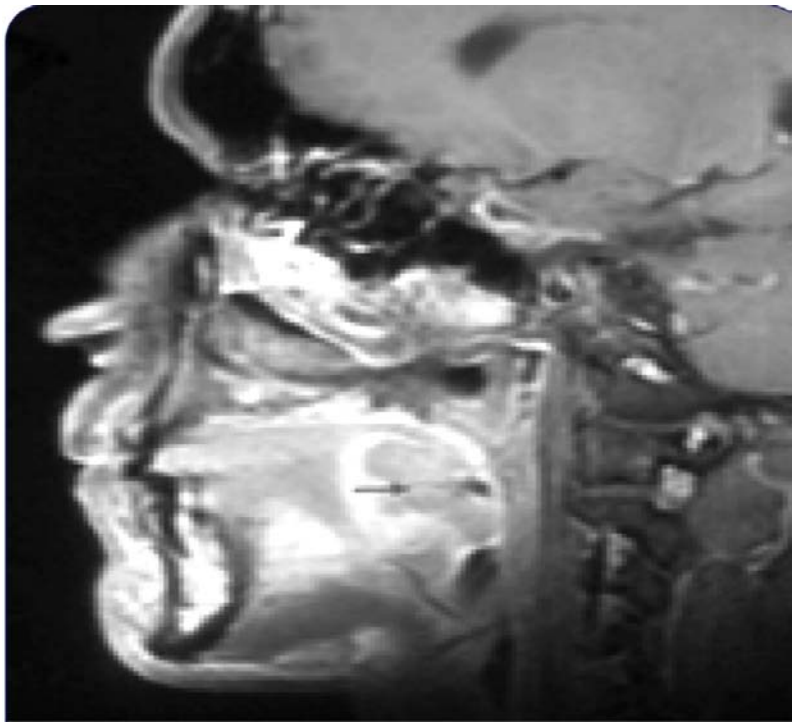

Figure 8: Sagittal cut of a Magnetic Resonance Imaging showing a mass in the base of the tongue

5.3. Intervention

A surgical biopsy was carried out. A histopathological examination and immunohistochemical staining revealed a well-differentiated squamous cell carcinoma (Figure 9). The tumor was classified as stage T1N0M0.

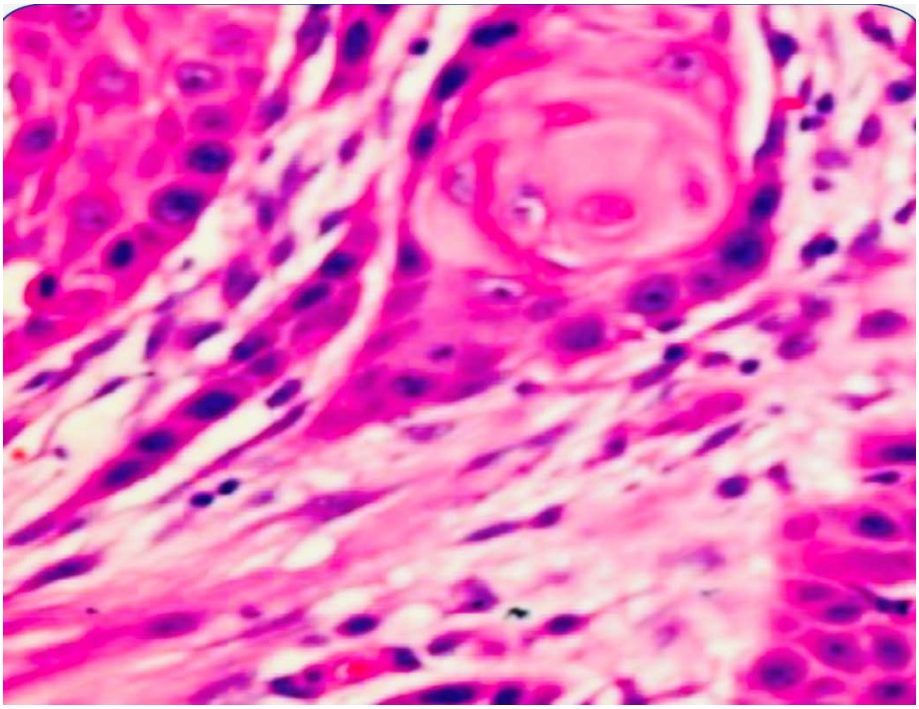

Figure 9: Histopathological appearance of squamous cell carcinoma of the tongue

5.4. Extension assessment

This procedure included the use of a chest-CT and an abdominal ultrasonography and did not find any distant metastasis.

5.5. Treatment

A multidisciplinary staff meeting was held wherein a surgical resection was opted for as the best treatment option. Surgery performed was with safe margins, without lymphadenectomy putting into consideration the difficulty of this entire operation on an irradiated tissue as well as the small size and the well-lateralized position of the tumor.

6. Progress of the patient after secondary malignancy

An 18 months follow-up showed the patient was without significant morbidity, assured as well that the patient was free of recurrence at a local or distant site.

III. Patient C

1. Description

An 85-year-old Moroccan man, retired from the army, married with a medical history of compensated hypertensive cardiomyopathy, hormonal and radiotherapy for adenocarcinoma of the prostate gland in 2014.

2. Adopted protocol

This protocol included the association of hormonotherapy and radiotherapy. Hormonotherapy by goserelin 10.8mg 1 injection/3 months and Bicalutamide 50mg 1 capsule/day for 1 month (15 days before goserelin injection and 15 days after) and radiotherapy at a total dose of 76 Gy, 2 Gy by fraction during weekdays for 8 weeks.

3. Duration of treatment

Three years of hormonotherapy and eight weeks of radiotherapy.

4. Progress of patient

A good evolution was observed. Unfortunately, the patient presented with a right thigh mass in 2020, 6 years after radiation therapy for prostate cancer, which was later on diagnosed as osteosarcoma.

5. Clinical findings, procedure and tests after secondary malignancy

5.1. Clinical presentation

The patient was stable on both respiratory and hemodynamic state, physical examination revealed an antero-extern and supra-trochanteric tumor mass of the right lower limb.

5.2. Laboratory tests

This revealed no anomaly except for normochromic normocytic anemia.

5.3. Imaging

A thoracic-abdominopelvic CT scan was done which showed the following, a dense right Medio-renal cyst (hemorrhagic cyst) (Figure 10). Hypertrophic and disorganized aspect of the iliac bone, evoking Paget's disease, the cuts passing through the thigh, revealed a voluminous tissue mass deep in the anterior loge, heterogeneous, enhanced in a heterogeneous way which happens to be the site of some calcifications measuring 11x16 cm, arriving near the femoral bone (Figure 11) associated with multiple neighboring and inguinal adenopathy, with the most voluminous measuring 12 mm.

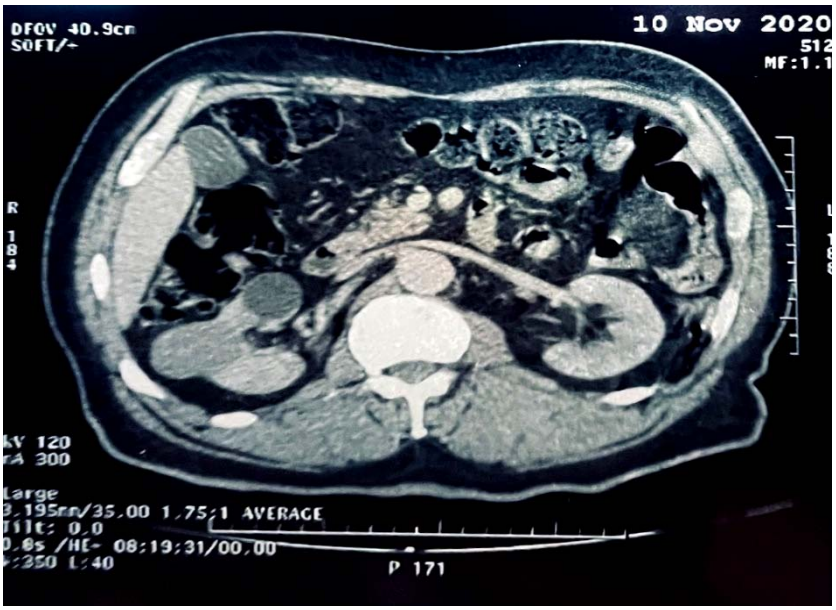

Figure 10: An axial cut of a CT scan passing through the abdominal region showing a right Medio-renal cyst

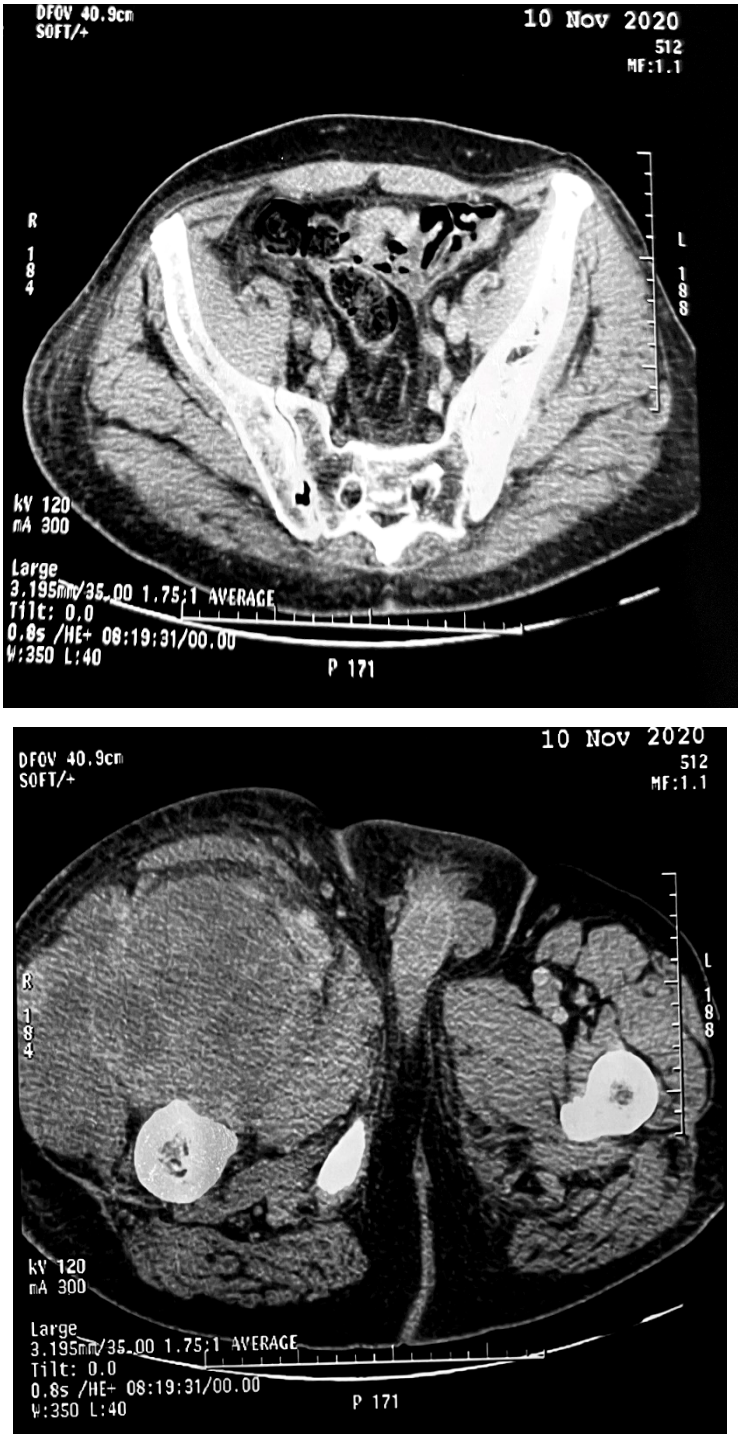

Figure 11: An axial CT scan cut passing through the pelvic showing a voluminous tissue mass deep in the anterior loge of the right thigh and a hypertrophic and disorganized aspect of the iliac bone

A right thigh MRI showed a locally advanced tumor lesion process of the muscles of the anterior and median loge of the right thigh, firstly evoking a neoplastic origin associated with bone extension (Figure 12). Right inferior limb Doppler echography showed an aspect in favor of right iliac-femoral-popliteal thrombophlebitis.

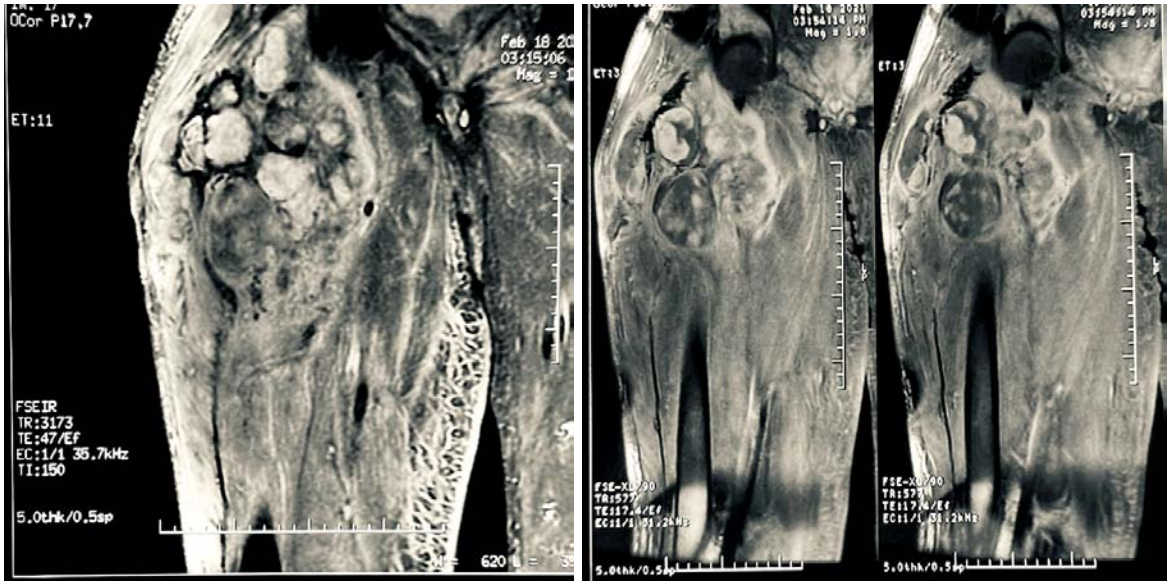

Figure 12 a : MRI frontal cut of the right thigh showing a Voluminous tumoral. process involving the vastus intermedius and lateralis very heterogeneous place of many components of varying signals remodeled, and necrotic

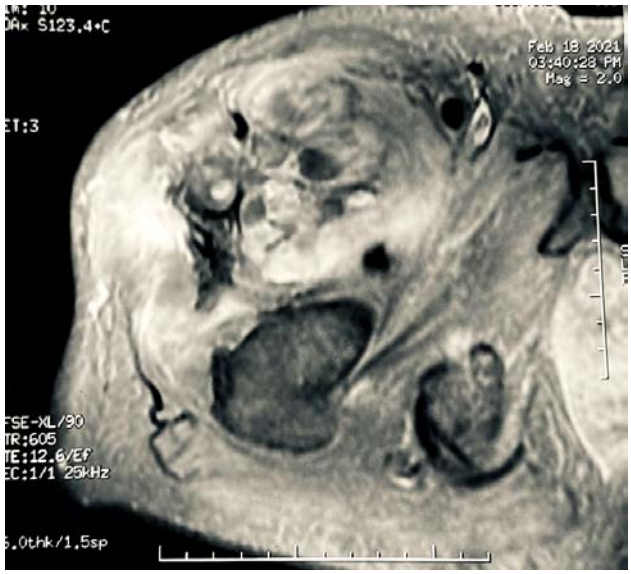

Figure 12 b: Axial cut of the MRI of the right thigh showing a very heterogeneous voluminous tumoral process involving the vastus intermedius and lateralis

5.4. Intervention

A surgical biopsy was performed, morphological aspect and immunohistochemical profile are in favor of a high-grade undifferentiated pleomorphic sarcoma.

5.5. Extension assessment

This was done by the use of a chest x-ray, thoracic-abdominopelvic CT scan which showed no distant metastasis. A multidisciplinary staff meeting was held shortly after to determine the modality of treatment.

5.6. Treatment

A multidisciplinary staff meeting was held during which it was decided the patient was ineligible for surgery due to the extension of the tumor, hence, chemo-radiation was opted for as the best treatment option. Chemotherapy was administered according to the AI (Ifosfamide-Adriamycin) regimen; Ifosfamide 3mg/m² per day for 3 days, Doxorubicin 60mg/m² once in addition with Mesna 3mg/m² and G-CSF followed up by a closure radiotherapy.

6. Progress of the patient after secondary malignancy

The patient's progress 16 months after secondary malignancy is marked clinically by asthenia and weight loss, laboratory tests revealed severe anemia which required several transfusions, renal insufficiency with urea at 0.74g/l and creatinine at 16.84mg/l, thoracic-abdominopelvic CT scan, showed stability of the disease, and an MRI of the right thigh, showed a partial response to the treatment (Figure 13).

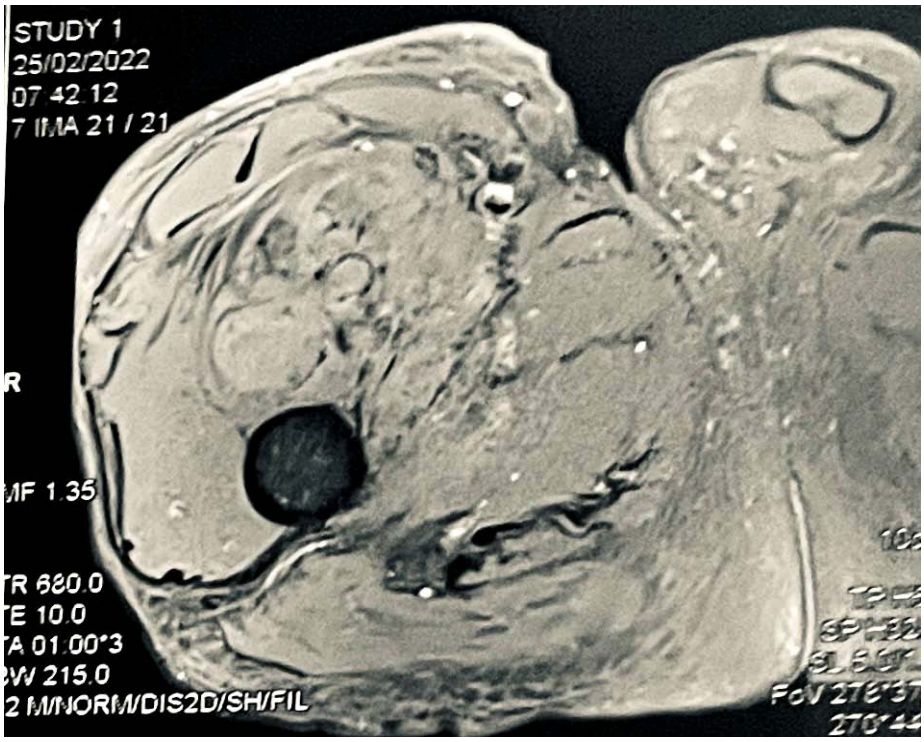

Figure 13: Axial cut of a thigh MRI showing partial response to chemo-radiation

Table 1: Summary of Patient's description

Description	Patient A	Patient B	Patient C
Age at primary malignancy	52	51	79
Sex	Male	Male	Male
Year of first malignancy	2007	2002	2014
Type of first malignancy	Squamous cell carcinoma of the right lung	Hodgkin's lymphoma of the Waldeiyer's ring	Adenocarcinoma of the prostate
Treatment of first malignancy	Concomitant chemo-radiation (Vinorelbine-cisplatin regimen and 60 Gy radiation)	Concomitant chemo-radiation (ABVD regimen and 36 Gy radiation)	Hormonotherapy (Goserelin + Bicalutamid) Radiotherapy 76 Gy
Time interval to second malignancy	10 years	14 years	6 years
Age at secondary malignancy	62	65	85
Type of second malignancy	Chondrosarcoma of the right scapula	Squamous cell carcinoma of the base of the tongue	Osteosarcoma of the right upper thigh
Treatment of second malignancy	Surgery only (surgical resection of the scapula and osteosynthesis of the right arm)	Surgery only without lymphadenectomy	Concomitant chemo-radiation (AI regimen and radiation)
Outcome	At 6 months post-surgery he had no complications nor recurrence	At 18 months post-surgery patient had no recurrence	At 16 months partial response to concomitant chemo-radiation

Table II: Summary of imaging and histopathological results after secondary malignancy

Imaging after second malignancy	Patient A	Patient B	Patient C
CT-Scan	tumor process on his right scapula, with sequela lung injury in the territory of the first tumor	-	-dense right Medio-renal cyst. -hypertrophic and disorganized aspect of the iliac bone, - Heterogeneous & voluminous tissue mass, with some calcifications measuring 11x16 cm. -multiple inguinal adenopathy, with the most voluminous measuring 12 mm.
MRI	-hyposignal at T1 and heterogeneous hypersignal at T2 centered on the supraspinous and infraspinous muscles measuring 90 mm on the longest axis and 60 mm on the shortest axis	mass of 1.5 cm diameter on the right edge of the tongue base with extension to adjacent structures	tumor lesion process of the muscles of the anterior and median loge of the right thigh, firstly evoking a neoplastic origin associated with bone extension
Scintigraphy	hyperfixation focused on the right scapula	-	-
SPECT-CT	osteocondensing and lytic aspect in the spine of his right scapula	-	-
Histo-pathological findings	Grade 1 chondrosarcoma	Well-differentiated squamous cell carcinoma. stage T1N0M0	high-grade undifferentiated pleomorphic sarcoma
Doppler Echography	-	-	Aspect in favor of right iliac-femoral-popliteal thrombophlebitis.

DISCUSSION

I. Generalities

Radiation-induced secondary malignancies (RISMs) are cancers that develop as a result of exposure to ionizing radiation. They can occur several years or even decades after the initial radiation exposure. The risk of developing a RISM depends on several factors, including the dose of radiation received, the area of the body exposed to radiation, and the person's age at the time of exposure (4).

The incidence of RISMs depends on the type of radiation therapy, overall dose, volume of tissue irradiated, and the type of cancer being treated (4). The incidence of RISMs is higher with high doses of radiation, with external beam radiation, and when the volume of tissue irradiated is large. Common types of RISMs include lung, breast, and thyroid cancer, as well as sarcomas and lymphomas. The risk of developing a RISM is higher in children and young adults than in older adults (4).

It is important to note that the benefit of radiation therapy in treating a primary cancer often outweighs the risk of developing a RISM. Radiation oncologist will take into consideration the risk and benefits of radiation therapy on an individual basis and will use techniques that minimize exposure to normal tissue and maximizes the dose to the tumor.

Preventive measures are also taken to minimize the risk of RISMs, such as using the lowest effective dose of radiation possible, limiting the area of the body exposed to radiation, and using advanced imaging techniques to more precisely target the tumor.

1. Definitions

1.1. Cancer

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. These abnormal cells can invade and damage nearby tissues and can spread to other parts of the body through the bloodstream or lymphatic system. Cancer is caused by

changes, or mutations, in the genetic material of cells. These mutations can occur spontaneously or as a result of exposure to environmental factors such as tobacco smoke, radiation, and certain chemicals. Some cancers can also be caused by viral or bacterial infections (5).

1.2. Radiation-induced secondary malignancies

Radiation-induced secondary malignancies are extremely rare and long-term radiotherapy complications that must be actively screened for due to the increased life expectancy of cancer survivors (4). This phenomenon is defined as the emergence of a secondary cancer following the use of radiotherapy to treat a primary cancer. Second cancers are distinct from primary cancers. It is important to note that secondary cancers can affect the same organ, but from different histological origins, or another organ entirely (6).

The classic criteria, first described by Cahan et al.(7) in 1948 for sarcomas in the bone territory, were used to confirm the diagnosis of radiation-induced cancer. These criteria were later extended to other tissue locations and non-sarcomatous radiation-induced tumors, and have now been unanimously modified. Thus, the extended criteria include the following elements.

- The tumor should be located in the irradiation field while taking into account the concepts of "threshold dose" and "dose-effect relationship."
- The second tumor's histology had to differ from the first lesions, or if it is a carcinomatous tumor, it had to rule out a metastatic tumor, a second location, a recurrence, or an evolutionary continuation. In this situation, the deciding factor would be the amount of time between the two cancers and their various locations.
- The appearance time should be longer than three years, with no upper duration limit (radiation-induced tumors can occur more than 30 years after the end of irradiation)

1.3. Radiotherapy

Radiotherapy, also known as radiation therapy, is a type of cancer treatment in which high-energy radiation is used to destroy cancer cells or shrink tumors. It is a non-invasive treatment that is given externally, typically with the help of a machine known as a linear accelerator, internally (brachytherapy) or systemically. The radiation beams are directed to the cancerous area while protecting the healthy tissues around it as much as possible. The goal of radiotherapy is to destroy as many cancer cells as possible while causing as little damage to healthy tissues as possible and this is achieved by radiation causing small breaks in the DNA inside cells (8). These breaks keep cancer cells from growing and dividing, hence, causing them to die. Radiotherapy can be used on its own or in conjunction with other cancer treatments such as surgery, chemotherapy, hormonotherapy and immunotherapy.

2. History of radiotherapy

Radiotherapy, also called Radiation therapy, is the use of high-energy rays or radioactive substances in the treatment of malignant or benign tumors, which is achieved by damaging their cells or halting their growth in a curative, palliative or symptomatic approach. The use of ionizing radiation and brachytherapy for treatments started shortly after the discovery of X-rays by Roentgen in 1895 and radium by Marie and Pierre Curie in 1898, respectively (9). The first use of X-ray was in the treatment of benign conditions such as lupus and eczema, and the earliest claim of using X-ray to cure cancer, specifically gastric carcinoma was in 1896, just 7 months after Roentgen's discovery (9). The use of radiotherapy alone or in association with other therapies dates back over 100 years in the treatment of cancer (10,11) and as of 2017, it was estimated that two-thirds of all cancer patients require radiotherapy uniquely or as part of a complex therapeutic protocol (10). In the early years after X-ray discovery, it was used to treat majorly skin cancer because of low penetrations in irradiated tissues however, this changed in the 1910s after Coolidge developed a new device capable of penetrating deeply into tissues by emitting higher energy X-rays (10,12).

In Morocco, Radiotherapy was first used in 1929 in Casablanca at the Centre de BERGONIE (13). In 2018, an article issued by the international atomic energy agency (IAEA) stated that about 17500 patients are treated annually by radiotherapy and an increasing demand is foreseen (14).

3. Dosimetry

"Dosimetry" refers to the science by which radiation dose is determined by measurement, calculation, or a combination of measurement and calculation. The technical name for radiation dose is "absorbed dose"; it is the amount of radiation energy that is deposited in tissue divided by the mass of the tissue (15). It is essential to study the dosage of ionizing radiation as this helps to prevent injuries and ensure optimum results. In the past, uncertain dosimetry led to a wide range of negative outcomes, which was amended in 1928 by the creation of Roentgen a unit of radiation exposure by the Second International Congress of Radiology (16–19). This step paved the way for the scientific development of the application of ionizing radiation for diagnosis and therapy. In recent years, a variety of radio-therapeutic equipment operating at accelerating voltages of about 50 kV to several million volts and producing beams of fast electrons as well as x-rays, such as the gamma-beam and x-ray equipment, has become widely available (16). The appropriate choice from these different radiation types has allowed for an increase in the radiation dose to targeted malignant cells and a decrease in the radiation dose to healthy tissues (16,20,21). The mechanism by which ionizing radiation causes significant see permanent damage to living tissue is by inhibiting the division ability of cells and if eventually attempted, cell death occurs (16). The increase in radiation dose notes a proportional increase in the volume of tumor and normal cells irradiated and stripped of their reproductive ability (16,22). Hence, a relationship between dose for tumor control and irreparable damage to healthy cells exists (16,22). For most tumors, and mammalian normal tissues, the dose-response curves tend to be of steep-sigmoid shape (Figure 14).

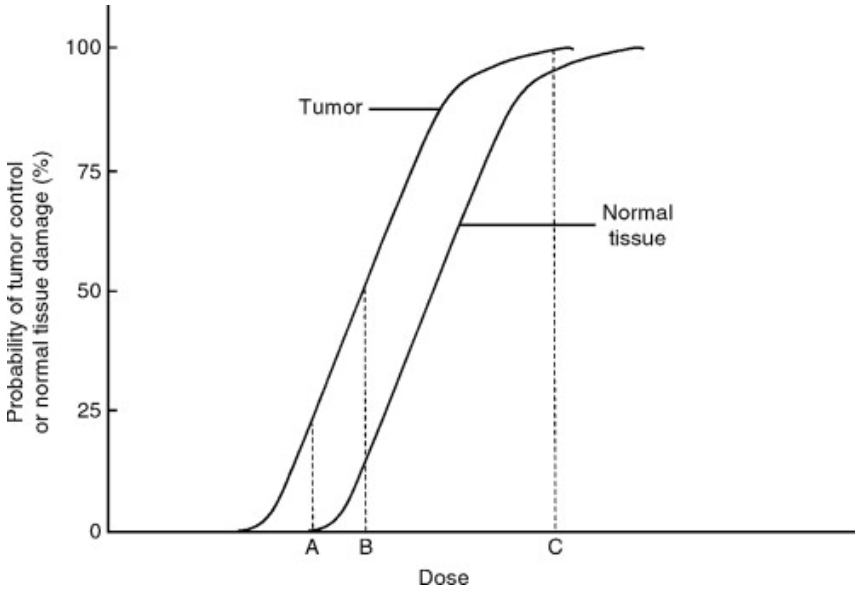

Figure 14: Hypothetical relationship between radiation dose and tumour cure/production of normal tissue damage. Dose A is associated with a lower probability of cure and a low probability of complications. An increase in dose (from A to C) would result in a higher cure rate, but at the expense of a higher complication rate (23).

The dose of radiotherapy is one of the determining factors of radiotoxicity but in itself is not sufficient alone to tell the degree of radiotoxicity to be expected in a particular individual. Other factors have been identified such as dose par fraction, volume irradiated, site of irradiation, dose inhomogeneity, additional treatment administered which could be concomitant chemotherapy or surgery, and an individual's radio-sensitivity which is an inherited trait and can only be genetically identified (16,22,24).

This study would not be complete without making a dive into fractionation. The radiation oncologist determines the optimal dose fractionation and this is patient-specific, after putting into consideration the patient's general health conditions, cancer type and its characteristics. Fractionation is the division of the total radiation dose to be administered into multiple fractions, which in turn seeks to maximize destruction to malignant cells while minimizing damage to healthy cells (21,25). This outcome is possible by the following mechanisms; redistribution, re-oxygenation and repair (25,26)

- Redistribution: most malignant cells are at different stages of their cell cycle and it has been shown that radio-sensitivity is highest at stage M and late G2. Hence, the deliverance of multiple fractions at intervals enhances the probability of achieving better tumor control (25,26).
- Re-oxygenation: hypoxic cells are less sensitive to the ionizing effects of radiotherapy. Dose fractionation allows oxygenated cells to be killed first while allowing time for the hypoxic cells to become re-oxygenated before subsequent fraction administration (25,26).
- Repair: healthy cells can repair their damaged DNA faster than malignant cells, so therefore, fractionation reduces the amount of radiation dose given by session and consequently gives healthy cells time to repair their damaged DNA as opposed to their counterpart malignant cells (25,26).

There are different methods of radiotherapy fractionation namely, hyper-fractionation, hypo fractionation, split course, and continuous hyper-fractionation accelerated radiotherapy (CHART).

In general, during a curative approach in Radiotherapy, a total dose ranging from 46 to 70 Gy is administered depending on the tumour location and characteristics, for 5 to 7 weeks with a daily dose of about 1.8 to 2 Gy given during weekdays, alongside a two-day break, usually on the weekends (21,27,28). These doses vary depending on the site and are limited by variable radiation injury to adjacent healthy tissues, with most gastrointestinal malignancies receiving 45-50 Gy, intrathoracic malignancies receiving 60-66 Gy, and prostatic and head and neck cancers receiving 70-80 Gy (29).

Meanwhile, for a palliative approach a shorter period of treatment is observed with a higher daily dose ranging from 3 to 8 Gy and a total dosage not exceeding 8 to 30 Gy (21).

4. Radiotherapy techniques

The widely available radiotherapy delivery methods are external radiotherapy, brachytherapy and metabolic radiotherapy.

4.1. External Beam Radiotherapy

This uses machines outside a patient's body to produce radiation beams targeted to destroy cancerous cells. External beam radiation often uses photons (x-rays) and sometimes protons and electrons. Photons and protons treat deep cancerous cells as well as those on the skin or in close proximity to it while electrons are used exclusively to treat superficial cancers. The most popular type of external beam radiotherapy machine is the linear accelerator LINAC (Figure 15). The types of external radiotherapy are conformal radiotherapy, intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), image-guided radiotherapy (IGRT), 4-dimensional radiotherapy (4D-RT), flash radiotherapy (FLASH-RT), proton beam therapy, stereotactic radiotherapy (SRT) and radiosurgery (SRS), adaptive radiotherapy, and superficial radiotherapy.

Figure 15: Linear accelerator LINAC (30)

4.2. 3D-Conformal radiotherapy (3DCRT)

This technique shapes the radiation beam to match the shape of the tumor and delivers radiation precisely to the tumor cells, hence, allowing the use of higher doses as it uses targeted information to focus radiation on the tumor, while avoiding the surrounding healthy tissues (31). (Figure 16)

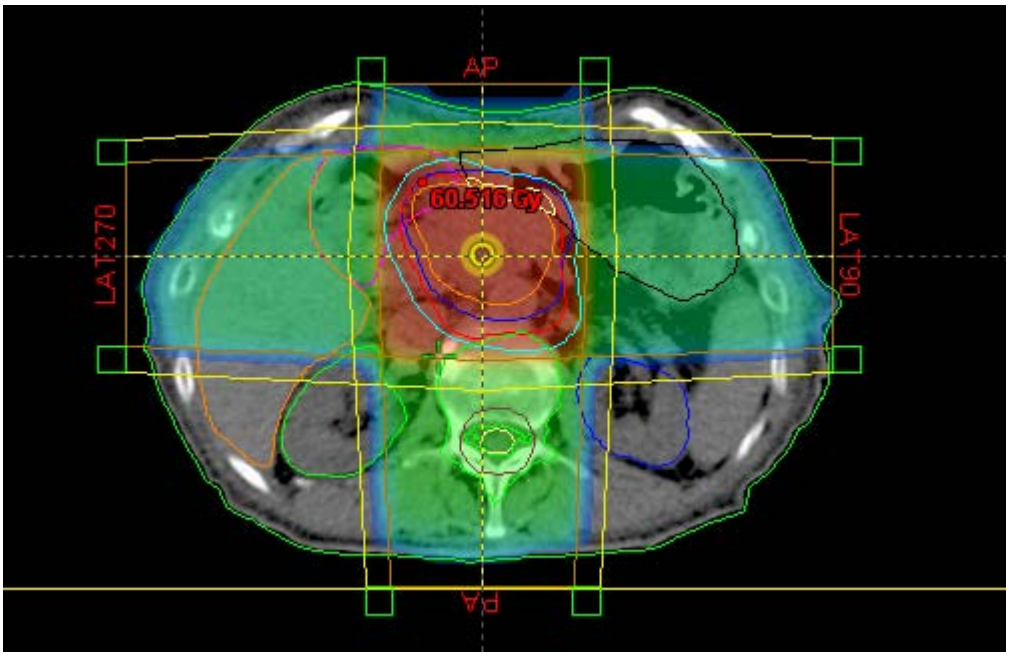

Figure 16: Dose distribution with 3DCRT (32)

4.3. Intensity-modulated radiotherapy (IMRT)

Intensity-modulated radiation therapy (IMRT) uses computer-controlled linear accelerators and is an advanced mode of high-precision radiotherapy, which delivers precise radiation doses to a malignant tumour or specific areas within the tumor. By modulating—or controlling—the intensity of the radiation beam in multiple small compartments, IMRT allows the radiation dose to conform more accurately to the three-dimensional (3-D) structure of the tumor. IMRT also allows higher radiation doses to be focused on the tumor while minimizing the dose to surrounding normal critical structures. Treatment is meticulously planned by using 3-D computed tomography (CT) or magnetic resonance imaging (MRI) of the patient in conjunction

with computerized dose calculations to determine the dose intensity pattern that will best adapt to the tumor shape. Typically, combinations of multiple intensity-modulated fields coming from different beam directions produce a customized radiation dose that maximizes the tumor dose while also minimizing the dose to adjacent normal tissues. Because the IMRT approach reduces the normal tissue dose-to-tumor dose ratio to a minimum, higher and more effective radiation doses can be safely delivered to tumors with fewer side effects than conventional radiotherapy techniques. IMRT can reduce treatment toxicity even when dosages are not increased. When compared to conventional radiotherapy, due to its complexity, IMRT requires slightly longer daily treatment times, additional planning, and safety checks before the patient can start treatment (33) (Figure 17).

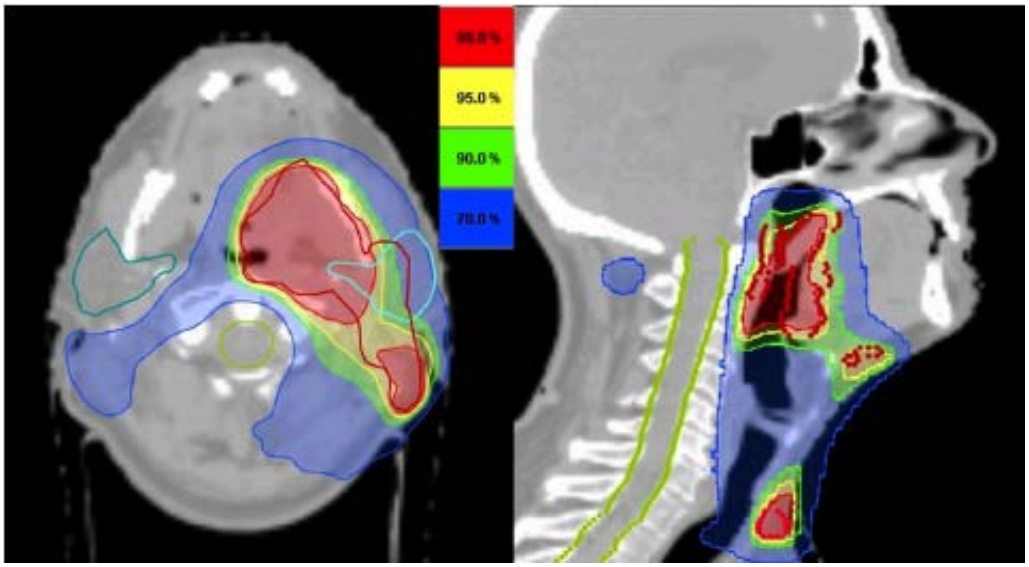

Figure 17: IMRT showing varying radiation intensities (34)

4.4. Volumetric modulated arc therapy (VMAT)

Volumetric modulated arc therapy (VMAT) is a type of external beam radiation therapy that uses multiple beams of radiation that are precisely aimed at the tumor from different angles. It is a form of intensity-modulated radiation therapy (IMRT) that delivers the radiation in a dynamic arc, allowing for more precise targeting of the tumor while minimizing exposure to healthy tissue. During VMAT treatment, the linear accelerator rotates around the patient,

delivering radiation from different angles. The radiation dose is modulated in real-time, meaning that the intensity of the radiation can be adjusted as the machine rotates. This allows a higher radiation dose to be delivered to the tumor while minimizing exposure to healthy tissue (35).

VMAT can be used to treat a wide variety of cancer types, including prostate, lung, head and neck, and brain cancer. It can also be used to treat benign tumors and it can be used alone or in combination with other types of cancer treatments such as surgery or chemotherapy. One of the benefits of VMAT is that it can shorten the treatment time and reduce the number of treatment sessions required when compared to traditional IMRT (35). It also can help to reduce the side effects of radiation therapy.

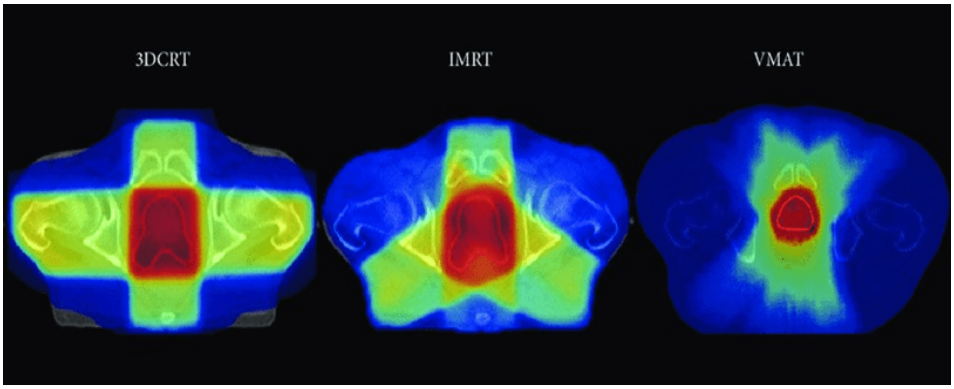

Figure 18: Comparison between various RT techniques (36)

4.5. Image-guided radiotherapy (IGRT)

Image-guided radiotherapy (IGRT) uses medical imaging to help provide precise and accurate radiation treatment. It can also be used to treat tumors in moving parts of the body, such as the lungs. Prior to treatment, the region to be treated will be scanned. These images aid in positioning and targeting radiotherapy to the tumor. To help further align and target the area during radiation treatment, certain IGRT procedures use special methods, such as fiducial markers or special techniques such as 4D gating. They may also use special devices to maintain the same position throughout each session (37). (Figure 19)

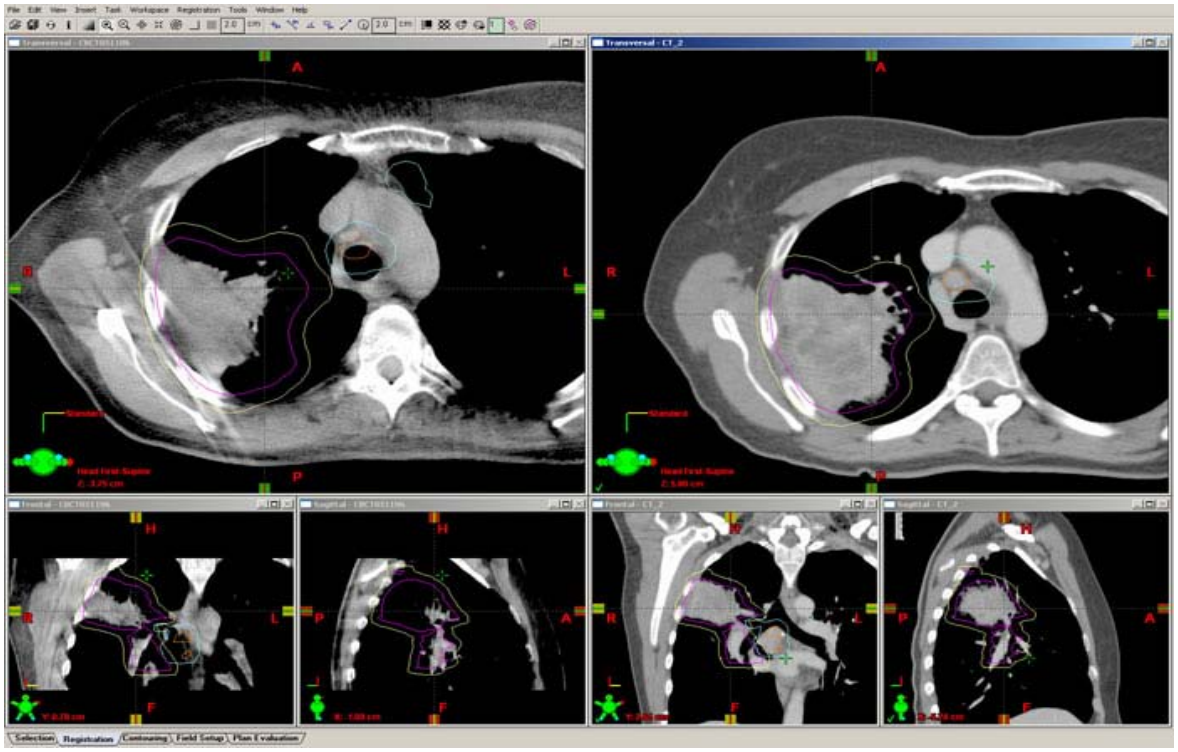

Figure 19: IGRT images taken daily before treatment to ensure accurate treatment placement(38)

4.6. Flash radiotherapy (FLASH-RT)

Flash radiotherapy (FLASH-RT) is a novel technique for treating tumors at ultra-high dose rates (›40 Gy/s) that actually reduces trauma to normal tissue surrounding the tumor while providing the same anti-tumor effect as conventional dose rate radiotherapy (CONV-RT) (39). However, the mechanism underlying the FLASH effect is poorly understood. The ultra-high dose rate radiation used in FLASH radiotherapy causes a phenomenon known as the FLASH effect, which lessens the typical tissue toxicities generally associated with conventional radiotherapy while maintaining local tumor control. The FLASH effect's underlying mechanism(s) have not yet been fully explored, however, the most recent viable theory places a major emphasis on oxygen tension and reactive oxygen species (ROS) production (39). The FLASH effect has been demonstrated in numerous studies in recent years, both in vitro and in vivo (40). FLASH radiotherapy was even used to treat the first patient with T-cell cutaneous lymphoma (41). However, the majority of FLASH radiotherapy studies have employed electron beams with low

tissue penetration, which poses a barrier to clinical practice adaptation. Proton beam therapy is a promising alternative to the FLASH delivery method because the dose can be deposited deeper within the tissue. Albeit, research into FLASH protons is currently limited (39).

4.7. Proton beam therapy (PBT)

To treat specific types of cancer, proton beam therapy uses a beam of high-energy protons, which are small parts of atoms, rather than high-energy x-rays (called "photons"). Proton beam therapy precisely targets a dose of high-energy protons at a tumor, reducing damage to surrounding healthy tissues and vital organs, which is advantageous in certain patient groups or when the cancer is close to a critical part of the body, such as the spinal cord. Proton beam therapy is only appropriate for certain types of cancer, such as highly complex brain, head and neck cancers, and sarcomas, because it does not improve outcomes for many cancer cases when compared to using high energy X-rays, which is still considered the most appropriate and effective treatment for the majority of cancers (42).

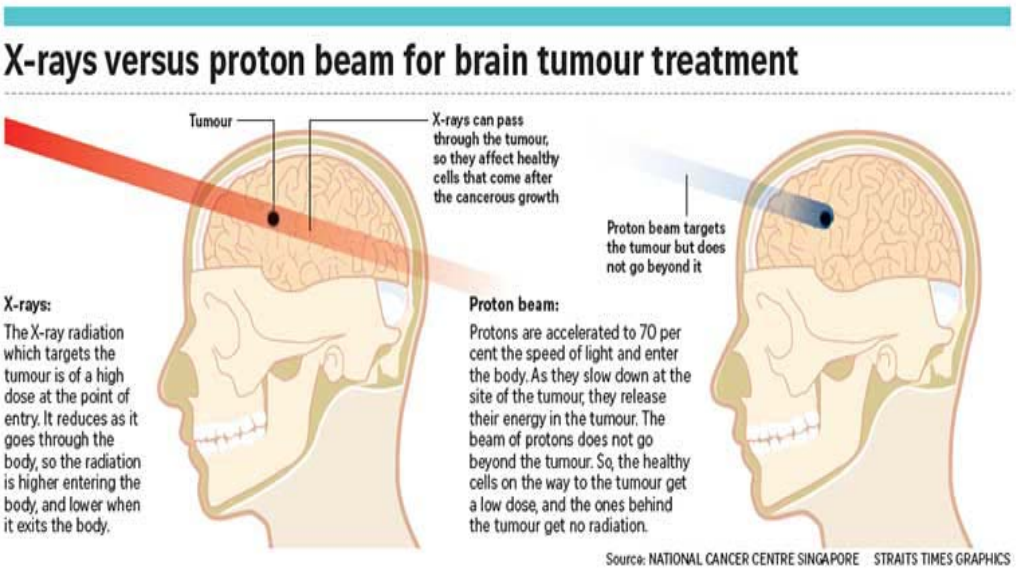

Figure 20: X-ray vs proton beam for brain tumour treatment (43)

4.8. Stereotactic radiotherapy (SRT)

Stereotactic radiotherapy (SRT) is a type of external beam radiation therapy in which high doses of radiation are precisely targeted to a tumor using advanced imaging techniques. The goal of SRT is to deliver a high dose of radiation to the tumor while exposing as little healthy tissue as possible. SRT typically involves the use of multiple radiation beams that are precisely aimed at the tumor from various angles. This allows for a higher radiation dose to be delivered to the tumor while protecting healthy tissue. A linear accelerator or a gamma knife machine can be used to deliver SRT. Stereotactic radiotherapy can also be used to treat areas of the body that have previously been treated with radiotherapy. For example, if someone has previously received radiotherapy to their pelvis, they are unlikely to be able to receive it again. However, because stereotactic treatment is so precise, re-treatment is frequently possible. Stereotactic radiotherapy to the brain might be called **stereotactic radiosurgery (SRS)** (44,45).

This type of radiotherapy is primarily used to treat very small cancers, such as lung cancer, cancer that began in the liver or cancer that has spread to the liver, cancers in the lymph nodes, spinal cord tumors, and brain metastasis (44,45).

Figure 21: Patient positioned to receive SRT (46)

4.9. Superficial radiotherapy

Superficial radiotherapy, also known as surface or skin-directed radiotherapy, is a type of external beam radiation therapy in which radiation is delivered directly to the skin or body's surface (47). It is used to treat skin cancers such as basal cell carcinoma and squamous cell carcinoma, as well as cancers that have spread to the skin from other types of cancer. A special machine called a superficial X-ray unit is used to deliver radiation in superficial radiotherapy. The machine is positioned close to the skin, and the radiation is directed at the skin cancer or other affected area. The radiation dose is typically low, and the treatment takes only a few minutes. Superficial radiotherapy can be used alone or in conjunction with other cancer treatments like surgery or topical chemotherapy. It is a highly effective skin cancer treatment that can be used to treat primary or recurrent tumors, as well as a palliative treatment for advanced cases.

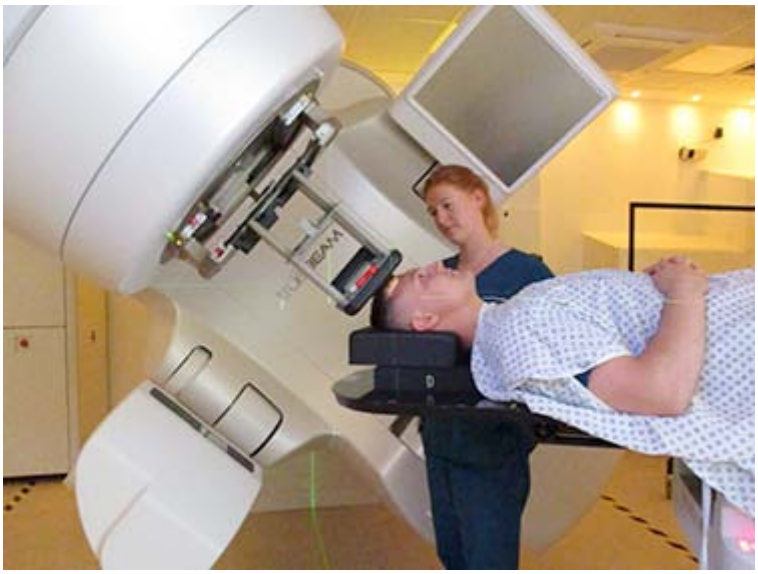

Figure 22: Superficial X-ray machine using low energy X-rays (48)

4.10. Brachytherapy

This radiotherapy technique requires the placement of radioactive material in the body close to or inside the organ to be irradiated. Radioactive sources used are thin wires, ribbons, capsules or seeds; these can be temporarily or permanently placed. Brachytherapy allows the

delivery of higher doses of radiation to more-specific areas of the body, compared with the conventional form of radiation therapy (external beam radiation) that projects radiation from a machine outside your body. Fewer side effects are noted, with an overall shorter treatment duration. This radiotherapy technique is often used for cancers of the prostate gland, cervix, uterus and vagina (49) (Figure 23).

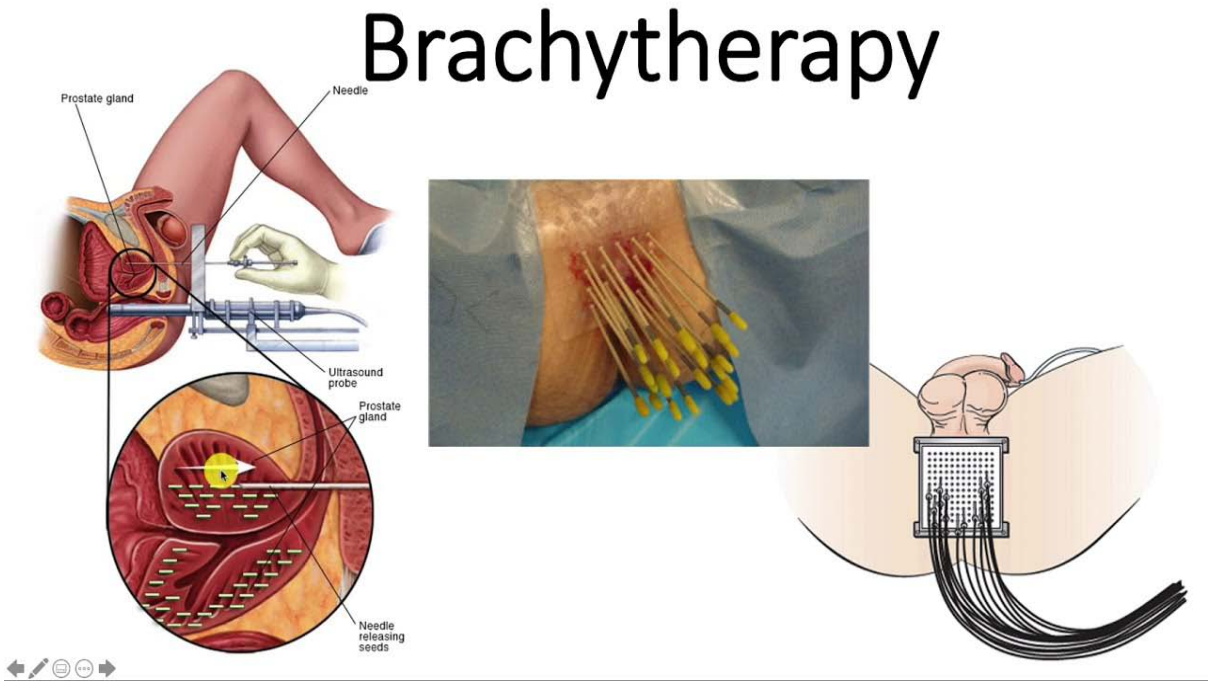

Figure 23: Brachytherapy procedure in prostate cancer (50)

4.11. Metabolic therapy

In this type of radiotherapy, radioactive compounds are introduced into the body, either intravenously or orally. The most significant case is the treatment of thyroid conditions by administering iodine-131, which is metabolized only in the thyroid (Figure 24), without affecting healthy tissues by destroying the malignant cells, thus preventing them from growing and reproducing (51).

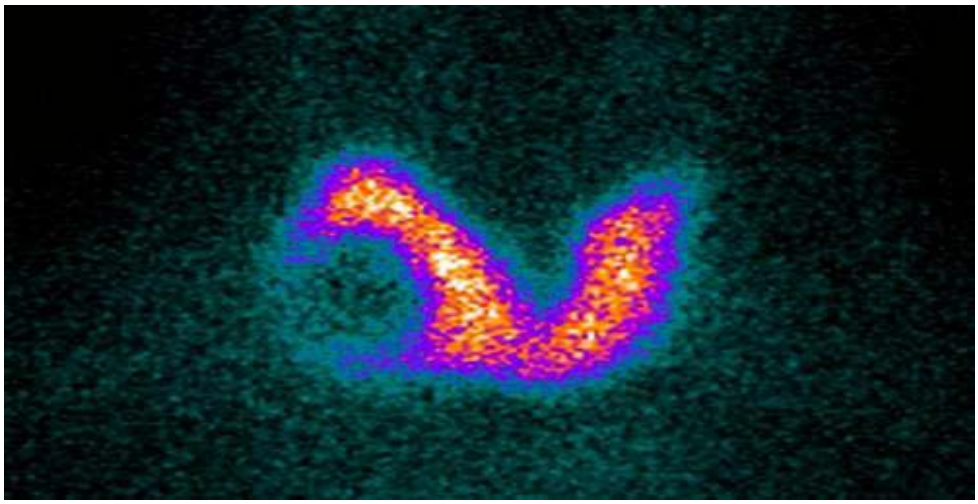

Figure 24: Image of the thyroid gland after administering iodine-131 (51)

5. Radiation-induced secondary malignancies

Data about radiation-induced malignancies dates back to the Atomic bomb survivors at Hiroshima and Nagasaki in 1955 (52). A subsequent increase in leukaemia was noted in the survivals of the atomic bomb attack 6-8 years after the bombings and the relative risk (RR) in a child irradiated at the age of 10 is 70 times more. Solid tumors were also recorded and there has been no decline in the incidence of the former as opposed to leukaemia as time passes.

In early clinical days, radiotherapy was used in minute doses for the treatment of non-oncologic diseases such as tinea capitis, acne, ankylosing spondylitis, hemangioma, and tonsillar hyperplasia (53). This resulted in an up rise in the incidence of developing solid tumors as well as hematologic tumors, leading to the abandonment of this practice.

Cancer survivors with a family history of cancer may be at an increased risk of developing a second malignant neoplasm (SMN). Individuals with a family history of cancer family syndrome (for example, autosomal dominant inheritance, early onset cancer, and clustering of cancer types) may be candidates for genetic testing and should be referred for genetic counselling (54,55). A cancer survivor who has a germline mutation in a cancer-causing gene is more likely to develop specific second primary cancers, and they may be eligible for high-risk screening and

prevention strategies (56). Hereditary breast and ovarian cancer, as well as hereditary nonpolyposis colorectal cancer, or Lynch syndrome, are the most common syndromes identified to date (57). BRCA1 and BRCA2 mutations are linked to an increased risk of second primary breast cancer or ovarian cancer (58,59). Mutations in mismatch repair genes (MLH1, MSH2, PMS1, MSH6) increase the risk of a number of cancers, including second primary colon cancer and other gastrointestinal and gynecologic cancers (60).

Dracham et al. (4) reported that after surviving a primary malignancy, 17%–19% of patients develop a second malignancy. SMNs now account for approximately 16% (or one in six) of cancers reported to the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) Program (61). Kuttesch et al. (62) estimated that at 20 years post-radiation, the estimated cumulative incidence rates for any second malignancy and secondary sarcoma were 9.2% (SD = 2.7%) and 6.5% (SD = 2.4%), respectively. According to Morton et al. (63), the cumulative incidence of all second cancers was 20.5% after 30 years from primary cancer diagnosis in childhood cancer survivors. The median time between the first and second cancer diagnoses was 17.8 years. The incidence of second cancers has become more common as the population of adult cancer survivors has grown and as the population has aged, rising from 9% of all cancer diagnoses in 1975–1979 to 19% of all cancer diagnoses in 2005–2009 (4). Hall et al. (64) reported that the lifetime risk of radiation-induced cancer per sievert for the female population is 15% for newborns, 10% for a 10-year-old girl, 5% for a 30-year-old woman, 2% for a 60-year-old woman, and almost nil for a woman over 80 years old.

Advances in early detection, supportive care, and treatment have resulted in an increasing number of cancer survivors, with a current 5-year relative survival rate of approximately 66.1% for all cancers combined diagnosed from 1999–2006 (61). The Childhood Cancer Survivor Study's follow-up data show that mortality due to second malignancies has increased over time when compared to mortality due to other causes at 25 years after the first cancer diagnosis (4).

Table III: Radiation-induced secondary malignancies

Study/year	Brenner et al. (65) 2000	Morton et al. (66) 2012	Liu et al. (67) 2020	Our study 2023
No of patients	51584	289748	41446	1575
Average age at primary malignancy (yr)	70.3	28-88	43	60.6
Latency period (yrs.)	5- >10 (range)	5-37 (range) 13 (median)	9 (mean)	10 (mean)
No of patients that developed secondary malignancy	3549	252	88	3
Average age at secondary malignancy (yr)	-	-	53	70.6
Incidence of secondary malignancy	6.8%	0.08%	0.21%	0.19%
Place of study	USA	Maryland (USA)	china	Morocco

6. Etiopathogenesis

The development of radiation-induced secondary malignancies (RISMs) is a complex and poorly understood process. It is thought to involve a combination of direct and indirect mechanisms.

The development of RISM is based on the mutagenesis of normal tissue caused by ionizing radiation (29). Direct tissue injury is characterized by DNA breaks; DNA damage in cells is one of the direct mechanisms by which ionizing radiation can cause cancer. Radiation can cause DNA mutations, which can result in uncontrolled cell growth and division and, eventually, the development of a RISM. Radiation-induced mutations can also lead to the formation of new blood vessels that supply the growing tumor, allowing cancer to spread to other parts of the body. Another direct mechanism is the production of free radicals by ionizing radiation, which

can damage the cell's DNA, lipids, and proteins. Furthermore, radiation can cause chromosomal aberrations, which can lead to cancer development.

The mechanism of indirect tissue injury is caused by oxidative damage from free radical formation. The bystander effect, which refers to the spread of radiation-induced oxidative stress from exposed cells to non-targeted cells via various intercellular communication mechanisms, increases the rate of spontaneous gene mutations in those cells and their progeny (29). Furthermore, the delayed effects of reactive oxygen and nitrogen species can last for months. These long-term effects could explain the latency period, which characterizes RISM development. The indirect mechanisms can also include changes in the cells' microenvironment, such as inflammation, which can promote the growth and survival of cancer cells. In addition, this can include immune system changes, such as immune cell suppression, which can make it more difficult for the body to detect and eliminate cancer cells. Carcinomas and leukemia are more common in areas that receive low doses of radiation or are far from the treatment site. Sarcomas, on the other hand, are more common in areas exposed to higher doses of radiation or in close proximity to the treatment site (29).

Although the mechanisms underlying RISM have been well characterized, the genetics of RISM is, with a few exceptions, poorly understood. Germline mutations in tumor suppressor genes such as TP53 and Rb have been found in soft-tissue sarcomas from RT patients. Radiation causes random mutations throughout the genome, whereas radiation-naive tumors have a heterogeneous density due to mutational hot spots. Some of these mutations are driver mutations, and some of these driver mutations are linked to specific types of RISM (24). MYC proto-oncogene amplification is found in nearly all RT-associated secondary angiosarcomas. Due to the other predominant confounding risk factors, including lifestyle and genetic predisposition that contribute to cancer pathogenesis, risk assessment for second malignancies in patients who received radiation therapy is still a contentious topic.

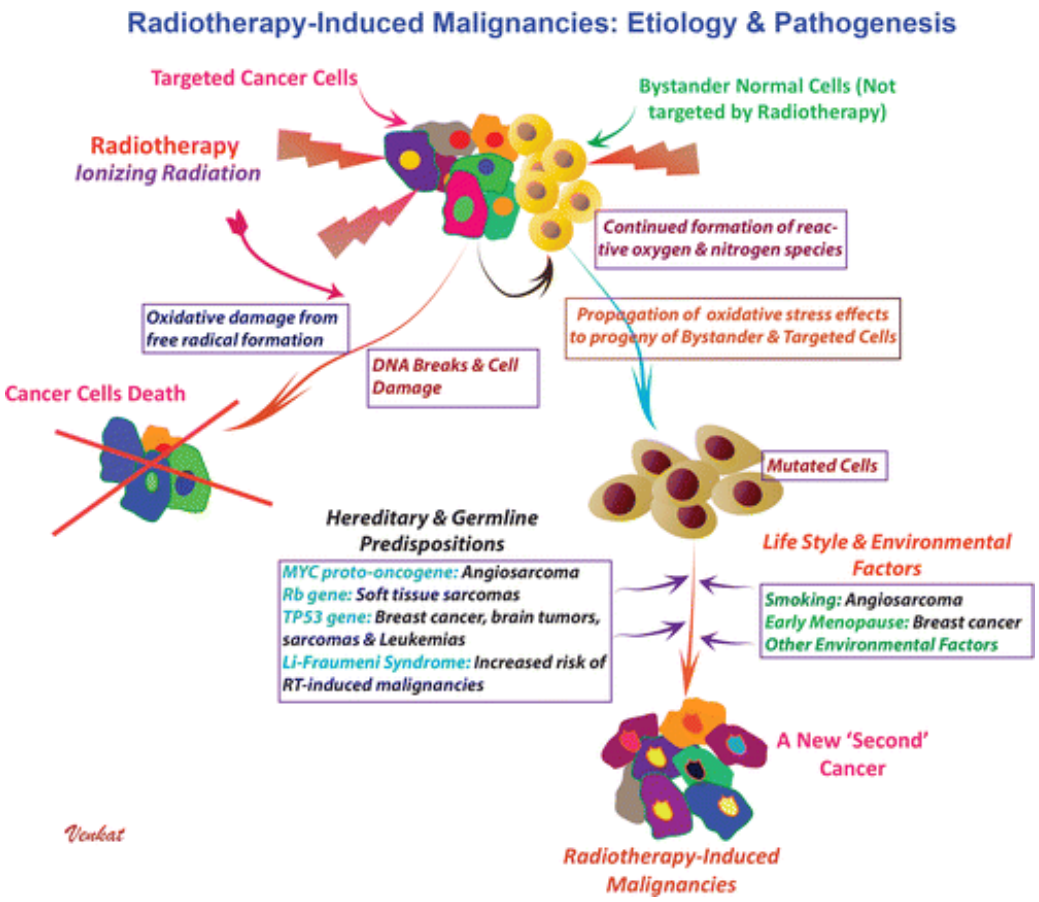

Figure 25: The diagram depicts the causes and pathogenesis of RISMs (29). Continued formation of reactive oxygen and nitrogen species, as well as the transmission of oxidative stress effects to the progeny of bystander cells, results in the development of mutated cells. After a long period of latency, these mutated cells develop into RISM under the influence of lifestyle and environmental factors, as well as hereditary predispositions.

II. Epidemiology

1. Frequency

The frequency of RISM is determined by several factors, including radiation therapy dose and fractionation, the volume of tissue exposed to radiation, and the time between primary cancer treatment and the development of secondary malignancy. The incidence of RISM has been estimated to be between 2 and 5 cases per 10,000 radiation therapy patients. Higher radiation

doses and longer exposure durations are associated with a higher risk of RISM, whereas lower doses delivered over longer periods are associated with a lower risk.

2. Age

The patient's age plays an important role in the development of RISM, with younger patients being more vulnerable than older patients. This is most likely due to younger patients' longer lifespan, which allows more time for the development of RISM (4,68). Other risk factors, such as smoking history or exposure to other forms of ionizing radiation, can also increase the risk of RISM.

3. Medical history

The patient's medical history is also an important factor in the development of RISM. Patients who have previously been exposed to radiation for another cancer or a benign condition, such as the treatment of an enlarged thyroid, are at a higher risk of developing RISM. Patients with a history of other medical conditions, such as autoimmune diseases or a cancer family history may be at a higher risk of RISM.

4. Risk factors of radiation-induced secondary malignancies

4.1. Age at radiation

Children are at a greater risk of developing secondary malignancies given a higher life expectancy alongside the long latency period to developing second cancer, also, children are more sensitive to radiation as compared to adults, thereby potentiating the risks or side effects expected after radiation exposure (4,69,70). Thirdly, most malignancies in children are related to a germline mutation reiterating the earlier mentioned genetics playing a role in radiation-induced malignancy susceptibility(64).

4.2. Sex

A feminine predominance is observed, and this can be attributed to the early development of breast and thyroid cancer, which is predominant in women as compared to their male counterparts and which in general, requires the use of radiotherapy alone or alongside surgery and or chemotherapy for treatment (4,70). According to data from atomic bombs, Females are more susceptible to radiation-induced cancers than males (4). This data states that each Gray (Gy) of radiation increases the risk of solid cancer by approximately 35% (90% CI, 28%–43%) in males and 58% (90% CI, 43%–69%). In addition, for solid cancers as a group, women had an absolute excess rate of second cancer than men (female to male ratio, 1.4; 90% CI, 1.1–1.8).

4.3. Genetic predisposition

In a study done by Meadows A.T. et al (70), genomic DNA was collected and studied to determine the variability in the capacity to repair DNA damage caused by radiotherapy. It also evaluated the possibility of family cancer syndrome in patients diagnosed with secondary malignancy and found that the overall risk of developing cancer in a sibling of a diagnosed SMN patient is greater than that of the general population. Other germline mutations, such as gene TP53 mutation-Li-Fraumeni syndrome (4,53,71), have shown an increased risk of developing SMNs after radiotherapy.

4.4. Lifestyle and Environmental factors

A subset of SMNs share etiologic factors, such as environmental and lifestyle influences such as tobacco use, excessive alcohol consumption, and dietary patterns. Tobacco use is one of the leading causes of many primary cancers, with well-established links between the lungs and upper aero-digestive tract cancers (oral cavity, stomach, pharynx, larynx, and oesophagus). Excessive alcohol consumption has been linked to cancers of the mouth, pharynx, larynx, oesophagus, colon, rectum, liver, and breast. Tobacco and alcohol have synergistic effects on upper aero-digestive tract cancers (72). Being overweight or obese increases the risk of

numerous types of cancer, including postmenopausal breast cancer, endometrial cancer, colorectal, esophageal, gallbladder, kidney, pancreas, and thyroid cancer (73).

Some studies have compared the development of SMNs in nonsmokers and smokers treated with post-mastectomy radiotherapy (PMRT), smoking has been highlighted as a major factor in developing lung cancer after radiotherapy for breast cancer (4,71,74). Menopause has been shown to reduce the occurrence of radiotherapy-induced breast cancer in Hodgkin lymphoma and childhood cancer survivors who received a chest RT (4) and pediatric patients who received radiation therapy close to menarche are more likely to develop breast cancer, implying that radiation is more carcinogenic when the breast is developing (37).

4.5. Radiotherapy technique

The use of older radiation techniques has been linked to an increased risk of RISM. Recently, there has been concern that increased use of intensity-modulated radiotherapy (IMRT) is linked to an increased risk of RISM. In the IMRT technique, a greater amount of normal tissue is exposed to a low dose of radiation, which may result in a higher integral dose and, as a result, a higher risk of RISM. Long-term follow-up data, however, are required to determine whether IMRT increases the risk of RISM. Image-guided radiation therapy is another technological advancement in RT (IGRT). The use of IGRT during setup verification contributes approximately 5%-20% of the total dose to normal tissues located outside the primary treatment field. The routine use of portal imaging or mega-voltage (MV) cone beam computed tomography (CT) may result in daily exposures of up to 100 mGy, which can increase the long-term risk of RISM (4,64,76,77).

4.6. Type of radiation

In a research by Chung et al. (78) Proton beam therapy (PBT) had a lower crude rate of second malignancies than photon therapy (7.5% vs. 5.2%). The Bragg peak is most likely caused by the dosage deposited by protons, which abruptly approaches the end of their range, whereas

the dose deposited by photons is nearly exponential. As a result, photon beam therapy's integral dose is 2-3 times larger than that of protons. After a median follow-up of 7 years (ranging from 3.9 to 10.3 years) in a prospective trial of 59 medulloblastoma patients who received PBT, no patient had a second tumor identified (79). It was then compared to a case-matched series of 43 patients who received photon therapy during the same time period. In the photon cohort, three patients developed RISM, whereas no patients developed RISM in the proton cohort(80). Neutrons are not commonly used in modern radiotherapy due to their high energy level and potential to cause significant damage to healthy tissues, which may increase the risk of developing radiation-induced secondary malignancies. Electrons are sometimes used in modern radiotherapy, particularly for treating superficial tumors or cancer that has spread to the skin. Electrons have a lower energy level than photons, so they deposit their energy over a shorter distance. This means that they are less likely to cause secondary malignancies in healthy tissues further away from the area being treated.

4.7. Site of radiation

Certain organs have been linked with increased incidence of RISM after RT and these include; cancer of the lungs, esophagus and sarcomas after RT for breast cancer (81-83). Cancer of the bladder, rectum, lungs and sarcomas after RT for prostate cancer (65). Cancer of the colon, rectum, anal canal, ovaries, uterus and other pelvic structures after RT for cervical cancer (84), gastrointestinal malignancies after RT for endometrial cancer (85). Cancer of the breast, lung, colorectal, thyroid, stomach and sarcoma after RT for Hodgkin's lymphoma (86), solid tumors and leukemia after RT for non-Hodgkin's lymphoma (87).

4.8. Dose of radiation

The radiation dose received is a risk factor for radiation-induced secondary malignancies (RISMs). The higher the radiation dose received, the greater the risk of developing a RISM. Grays (Gy) are commonly used to measure radiation doses. Most studies show that secondary cancers

are observed majorly in regions adjacent to the targeted volume at an intermediate dose level, of 5 to 50 Gy (64,77).

4.9. Chemotherapy

This is known for its potential in causing secondary malignancies such as lung, thyroid, gastrointestinal and bladder cancer as well as sarcoma, especially after using alkylating agents(88). Alkylating agents, topoisomerase-II inhibitors and antimetabolites have the highest leukemogenic potential (4). According to Sylvie Guérin et al. (89), concomitant chemo-radiotherapy was found to significantly increase the risk of an SMN when compared to sequential chemo-radiotherapy, even after adjusting the local dose of radiotherapy and chemotherapy. Other studies also affirm an increase in RISM after concomitant chemo-radiation (88,90).

III. Literature review

In this segment of our study, we are going to discuss in detail our clinical cases in comparison to clinical cases available in the literature.

1. Patient A and Patient C

Patient A presented with chondrosarcoma of the scapula 10 years after radiotherapy for lung cancer. Patient C presented with osteosarcoma of the right lower limb 6 years after RT for prostate cancer. Chondrosarcoma is a rare type of malignancy that often begins in the bone or soft tissues surrounding the bones. It happens mostly around the pelvis, hip or shoulder, and rarely in the vertebral column. They are the second most common primary bone malignancy after osteogenic sarcoma. Chondrosarcomas are rare after RT, and are even rarer after RT for non-small cell lung cancer, and this can be attributed to its aggressive nature, with a limited survival rate that rarely exceeds 3 years after diagnosis (91). Chondrosarcomas are classified by histologic type (conventional, mesenchymal, clear cell, myxoid, and, the most malignant,

dedifferentiated) as well as grade (I-III, based on cellularity and nuclear enlargement and irregularity) (92). Chondrosarcoma accounts for only 3.7% of all radiation-induced sarcomas (RISs) (93,94). The incidence of secondary chondrosarcoma was estimated by Davies, Brett W et al.(92) in 2014 to be between 0% and 3.3%. They reported two cases of radiation-induced dedifferentiated chondrosarcoma with a mean latency period of 35.5 years following external beam radiotherapy for retinoblastoma and crânio-facial fibrous dysplasia. In 2015, Obid et al.(95) reported a case of dedifferentiated intra-spinal chondrosarcoma 18 years after RT for cervical carcinoma and death occurred 6 months after the patient's initial visit to the clinic.

Osteosarcoma is a type of cancer that begins in the cells that form long bones; it is the most common type of primary bone cancer. Radiation-induced osteosarcomas are very rare entities with extremely poor prognosis and increased mortality as opposed to primary osteosarcoma. This is due to the late diagnosis and often metastatic state at discovery, the location and size of the tumor, the difficulty of surgery, and the impossibility of giving full radiotherapy in previously irradiated tissues. The incidence ranges from 0.01% to 0.03% for all irradiated patients and 5.5% for all osteosarcomas (96). The occurrence of osteosarcoma specifically after radiotherapy for prostate cancer is extremely rare, however, in the case of an occurrence a 50% mortality is recorded within the first year after diagnosis.

Phillips and Sheline estimated a 0.23% frequency of sarcomas after breast cancer irradiation (97). According to Mark et al, the absolute risk of developing RIS after radiation therapy for gynaecologic malignancies is 0.03 % to 0.8% (98). After irradiation for any purpose, Amendola et al. reported an estimated incidence of sarcomas of 0.09 to 0.11% (99). According to Huvos et al. and Souba et al., 5% of sarcomas develop after therapeutic or accidental irradiation (100-102). Strong et al reported that the cumulative risk of a secondary sarcoma 10 years after Ewing's sarcoma approached 35%. Similarly, the Late Effects Study Group reported a 20-year estimated cumulative incidence of secondary sarcomas after Ewing's sarcoma of 22%.

Radiation-induced sarcomas have a poor prognosis in general. Arlen et al. reported a 5-year survival rate of 30% (103). Huvos et al. described 66 patients with post-radiation

osteosarcomas of bone and soft tissues in various sites. The 1-year cumulative survival rate was 50%, and the 5-year survival rate was 17% (104). Weatherby et al. reported a long-term survival rate of 30% in patients with long bone lesions of the extremities who were treated solely with surgery. When all sites were considered, however, the 5-year disease-free survival rate was only 19% (102). Centrally located XRT sarcomas have a worse prognosis than extremity sarcomas (7,101,103,105). All of the patients with XRT Sarcomas of the Chest Wall reported by Arlen et al.(103) and Huvos et al.(101) died as a result of metastases. Senyszyn et al.(105) and Hardy et al.(106) reported patient survival ranging from 3 to 24 months in their reviews of radiation-induced sarcomas that appeared after treatment for breast cancer. Almost all of these patients died as a result of metastatic sarcoma. According to Liao et al. (107), the 1-, 2-, and 3-year actuarial Overall Survival rates for patients with radiation-induced osteosarcoma of the mandible and maxilla (RIOSM) were 53.3%, 35.6%, and 13.5%, respectively. Furthermore, all patients died within 5 years of being diagnosed with RIOSM.

Studies on the impact of radiation therapy on bone have revealed that doses above 3,000 rads typically induce irreversible damage to the reparative processes and that dosages above 5,000 rads are likely to cause full devitalization of adult bone, but that higher doses may be more tolerant in children. Given that doses above devitalizing levels were administered to many individuals, it must be assumed that the lesions that resulted emerged at the fields' edges where levels were insufficient to eradicate all viable cells (103). Kuttesch et al. (62) reported that after radiotherapy for Ewing's sarcoma, there were no secondary sarcomas in patients who had received less than 48 Gy, whereas the absolute risk of secondary sarcoma in patients who had received ≥ 60 Gy was 130 cases per 10,000 person-years of observation.

Table IV: Average latency period for sarcomas

Study/year	Lagrange et al 2000 (108)	Coca-Pelaz et al 2020 (109)	Smith et al 2022(110)	Our study 2023
Average latency period (yr)	12	11.1	10.3	10

2. Patient B

Patient B presented with squamous cell carcinoma of the tongue 14 years after RT for Hodgkin's lymphoma. A carcinoma is a type of cancer that originates in the epithelial cells, which are cells that line the surface of organs and glands in the body. Carcinomas can occur in many different parts of the body, including the lungs, breasts, prostate, and colon. They are the most common type of cancer, accounting for about 80% to 90% of all cases of cancer (111). Tongue tumors brought on by radiation therapy for Hodgkin's disease are extremely uncommon. Some authors claimed that this uncommon consequence has become more common recently, particularly as a result of the patients' increased survival and prognosis following radiotherapy. It is difficult to pinpoint the precise pathogenic pathways that cause radiation-induced carcinomas. However, defined diagnostic standards exist (7). Dai et al. (112) reported that the incidence of secondary oral squamous cell carcinoma (OSCC) was uncommon after radiotherapy for nasopharyngeal carcinoma (NPC) and less than 5%. Zhang et al. (113) estimated the crude incidence of tongue squamous cell carcinoma (TSCC) after radiotherapy for NPC to be around 0.13%. Wolden et al. (114) reported the long-term monitoring results of 694 children and teenagers after Hodgkin's disease treatment and observed that 93% of second solid malignancies developed in areas that had received at least 35 Gy. Some researchers have reported a persistent increase in the relative risk of solid tumors after Hodgkin's disease (114-116) whereas others have reported a decrease in relative risk but a continued increase in absolute estimated risk (AER) (117,118). The overall Survival at 3 and 5 years was 60.3% and 39.4%, respectively for the Second primary oral squamous cell carcinoma after radiotherapy(119). Sun et al (120) estimated that the 3-year and 5-year overall survival (OS) was 56% and 43%, for second primary squamous cell carcinoma of the tongue after radiotherapy for nasopharyngeal carcinoma.

Song et al. (119) reported that the 5-year OS of patients with secondary oral squamous cell carcinoma (OSCC) is 39.4%, which is significantly lower than the 5-year OS of patients with sporadic lesions reported in the literature, also only margin status was a significant independent

prognostic factor of OS. Whereas, Dai et al. (112) reported that second primary OSCC had a worse outcome in nasopharyngeal carcinoma (NPC) survivors than sporadic OSCC.

IV. Clinical study

1. Clinical signs

There are no general clinical signs associated with radiation-induced secondary malignancies. However, special care should be taken in the case of any abnormality along the irradiated volume, especially after a long latency period after radiotherapy.

2. Imaging methods

Imaging is critical in the diagnosis, staging, and monitoring of RISMs. A radiologist is frequently the first person to suspect second tumors in a patient who has had radiation therapy for a primary tumor. These imaging methods range from an X-ray, ultrasonography, mammogram, CT-scan, MRI and PET-Scan. With CT-scan and MRI being the gold standard methods.

3. Pathological findings

A core needle biopsy is required to confirm the diagnosis. The biopsy will determine whether there is a new malignancy, a recurrence of the primary malignancy, or post-operative or post-radiotherapy changes. A biopsy will also reveal the disease's histologic subtype and grade.

4. Treatment modalities

Second primary tumors after irradiation have been widely reported to be more advanced, highly lethal, and resistant to standard treatment regimens. Liao et al. (107) proposed that the poor results were caused by the following factors:

- Delayed detection in previously irradiated tissue;
- Compromised resection margins due to tumor proximity to critical structures;
- Limited treatment options in a maximally irradiated field (i.e., technical difficulties of operating within an irradiated field and difficulties with irradiating the field with surrounding normal tissues that have been treated to near tolerance);
- Poor tumor sensitivity to chemotherapy;
- The high-grade nature of the vast majority of radiation-induced osteosarcoma (RIOS); and - host immunosuppression caused by a combination of tumor-related factors and previous treatment.

The treatment of RISM is frequently difficult and multidisciplinary, with a wide range of therapeutic options available. The type and stage of the cancer, the patient's overall health, and the treatment goals all influence the choice of treatment. RISM treatment options include surgery, radiation therapy, chemotherapy and symptomatic treatments.

4.1. Surgery

The preferred treatment for a localized tumor is a radical resection with negative histological margins. Surgical resection may include techniques such as wide excision, limb-sparing surgery, or forequarter amputation. The use of irradiation in the past has impeded the visualization of anatomic and tumor planes, thereby making it crucial to perform an aggressive and wide resection. A positive surgical margin has been shown to decrease patient survival by nearly 50%. Reconstruction may be necessary and may involve plastic surgery techniques such as split-thickness skin grafting, local flaps, or free tissue transfer. In some cases, a polypropylene mesh and methyl methacrylate sandwich technique may be used for the reconstruction of the chest or abdominal wall. Surgery can be performed alone or in association with chemotherapy or radiotherapy. In our study, two of the patients underwent surgery alone without adjuvant therapy.

4.2. Radiotherapy

Additional radiation therapy using modern techniques may be considered, but there are concerns about toxicity, as repeated high-dose radiotherapy is frequently impossible due to limited bone marrow function. The difficulty re-irradiation poses often requires a combination with chemotherapy. Majeed and Gupta (3) proposed a re-irradiation strategy for radiation-induced malignancies

- Informed consent and proper documentation
- Highly conformal and informed radiotherapy e.g. stereotactic radiotherapy, IMRT, proton therapy
- Calculation of biological effective dose(BED) is mandatory
- Use of 2 Gy or lower (hyper-fractionation)
- Control of diabetes and hypertension if any
- Management of radiation complications in a timely manner
- Organizational structure

  -institutional guidelines for tolerance doses

  -institutional program of quality assurance

  -late effect clinic

4.3. Chemotherapy

Palliative chemotherapy is the primary treatment option in cases of metastatic disease. Prior to surgical resection, chemotherapy may be used in a neoadjuvant setting to improve local control and eliminate subclinical metastatic disease. This approach has the potential to improve outcomes and increase the likelihood of successful surgical intervention. It is important to note that the type and stage of the disease, as well as the patient's overall health and treatment goals, must all be carefully considered and tailored to each individual patient. To achieve the best results, multiple agents in combination or sequential regimens may be required. Palliative chemotherapy aims to relieve symptoms, slow disease progression, and improve quality of life.

Anti-angiogenic drugs, such as sorafenib and sunitinib, have demonstrated some effectiveness in treating angiosarcomas. In our study, the AI (Ifosfamide-Adriamycin) regimen was used for one patient in association with radiotherapy.

4.4. Symptomatic treatments

The symptomatic treatment for radiation-induced second malignancies focuses on managing the symptoms and effects of the underlying cancer in order to improve the patient's quality of life. The following are some of the approaches that may be used for this purpose:

- **Pain management:** Cancer-related pain can be managed with pain relief medications such as opioids or nonsteroidal anti-inflammatory drugs (NSAIDs).
- **Symptomatic relief**: Specific cancer-related symptoms such as nausea, vomiting, or breathing difficulties may be treated with appropriate medications or other treatments to alleviate the patient's discomfort.
- **Supportive care**: Rehabilitation, psychological counselling, or palliative care may be provided to assist patients in managing their symptoms and improving their quality of life. For example, rehabilitation may help the patient regain physical function, psychological counseling may help the patient manage stress and anxiety, and palliative care may help the patient manage pain and other symptoms.

5. Screening

In general, all cancer survivors should follow applicable national cancer screening guidelines, such as those provided by the American Cancer Society (ACS), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), the National Comprehensive Cancer Network (NCCN) and the U.S. Preventive Services Task Force (USPSTF).

Table V: Suggested Screening for SMNs for Cancers Survivors at Moderate to High Risk (61)

CANCER SITE	RISK LEVEL	RECOMMENDATION
BREAST	**Moderate risk**: family history of breast cancer	-Mammogram starting 5 to 10 years before earliest case of cancer in the family; CBE twice yearly; BSE monthly
	High risk: Personal or family history of BRCA1, BRCA2, TP53, or PTEN mutation,	-Screening breast MRI, starting at age 25 years (or for women with a history of chest radiation, 5 to 10 years after radiation); annual mammogram; CBE twice yearly, BSE monthly
	History of radiation to chest between age 10 and 30 years	-Annual mammogram CBE twice yearly; BSE monthly
COLON	**Moderate risk** -FDR with colon cancer younger than age 60 years or two SDRs with colon cancer at any age	Colonoscopy -At age 40 years or 10 years before the earliest case of cancer in the family
	-Radiation in which colon/rectum were included in treatment fields	-At age 35 years or 10 years after radiation
	High risk -High-risk family history suggestive of HNPCC	-Colonoscopy every 1 to 2 years, starting at age 20 to 30 years (depending on syndrome)
OVARY	**High risk** -family history of ovarian cancer; personal history or family member with mutation in BRCA1 or BRCA2 or mismatch repair gene (MLH1, MSH2, MSH6, PMS2	-Serum CA125 and TVUS every 6 to 12 months, starting at age 35 years

Table V: Suggested Screening for SMNs for Cancers Survivors at Moderate to High Risk (61)(...)

CANCER SITE	RISK LEVEL	RECOMMENDATION
ENDOMETRIUM	High risk -family history suggestive of HNPCC	-Endometrial sampling annually starting at age 35 years
SKIN	High risk -family history of early melanoma	-Annual skin examination and monthly skin self-examination
LUNGS	Increased risk -prior radiation to chest with or without chemotherapy High risk -current smokers (›30 pack years); former smokers (›30 pack years and quit <15 years ago)	-Smoking cessation -Annual low-dose spiral CT
PROSTATE	High risk -Family history of early prostate cancer (onset younger than age 65 years); personal or family member with mutation in BRCA1 or BRCA2	-Serum PSA with or without DRE every 1 to 2 years, starting at age 45 years

NOTE: This table summarizes general follow-up recommendations for cancer survivors at moderate to high risk for second malignant neoplasms (SMNs).

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination; CT, computed tomography; DRE, digital rectal examination; FDR, first-degree relative; HNPCC, hereditary nonpolyposis colon cancer; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; SDR, second-degree relative; TVUS, transvaginal ultrasound.

V. Recommendations to reduce or prevent the occurrence of radiation-induced secondary malignancies (77)

1. Age consideration

During radiotherapy in children, the danger of radiation-induced cancer must unavoidably be a primary worry; in the case of teenagers and young adults, this risk must still be taken into consideration when deciding on a course of treatment. Radiation-induced cancer is significantly lower in adults and can almost be ignored in the elderly.

This idea of "risk" can sometimes determine the therapeutic protocol for children; in some (rare) instances, this risk may even cause radiotherapy to be discontinued. Instead, oncologists may opt for one or more non-irradiating treatments that are still effective as long as they do not compromise cure rates. In some instances, treatment combinations (particularly concomitant chemo-radiotherapy), will drastically lower the dose and the volume that needs to be exposed to radiation.

When radiotherapy is unavoidable for a child, every effort should be made to reduce the volume to be irradiated and to avoid and/or protect particularly critical organs such as the breast, thyroid, and encephalic structures. In these often difficult situations in children, protons can find, in certain cases, a place of choice; despite their neutron component, protons are often effective in limiting the impact of the input beams and exit, and to better target the tumor thanks to the Bragg peak.

2. Reduction of irradiated volumes

The reduction in irradiated volumes will inevitably result in a reduction in the regions receiving "intermediate" doses (a few grays), which have been shown to be the primary sources of radiation-induced cancers.

The radiation oncologist must therefore bear in mind the risk of radiation-induced cancers when he chooses his irradiation volumes. In a very young child, the organs at risk are

less distant and special attention must be paid. For example, abdominal irradiation can provide a significant dose in breast buds in a child under 3-4 years old. The extension of these volumes must imperatively be justified. Thus, wide irradiation of the pelvic lymph node areas for a patient at low risk of prostate cancer has no reason to be. Partin's table, Roach's formula, and nomograms available now give a fairly precise idea of the risk of lymph node involvement, and it is accepted that irradiation of lymph node areas is not justified below a theoretical risk of 15%. Similarly, the risks of lymph node irradiation breast cancer are now better defined, allowing patients to avoid both deterministic and radiation-induced cancers. The European Organization for Research and Treatment of Cancer (EORTC) trial on internal mammary chain irradiation is a typical example of the search for the best possible adaptation of the volumes to irradiate.

3. Radiotherapy technique adaptation

There has been an ongoing debate on the possibilities of certain modern radiotherapy technique increasing the risk of developing RISM. IMRT is known to be more precise in delivering higher doses to the tumor as compared to 3D-CRT however, more healthy tissues are exposed to low-dose radiation and this has been the argument of some authors in the possibility of these modern techniques being linked to higher radiotherapy-induced malignancies (64,77,121). On the other hand, Xiang et al (122) stated that there is no difference in the risk of developing a RISM following 3D-CRT or IMRT.

Proton therapy is another advanced radiotherapy technique that is designed to reduce the risk of RISMs. This technique uses beams of protons to deliver a highly precise and targeted radiation dose to the tumor while minimizing exposure of normal tissue. Proton therapy is particularly beneficial for high-risk patients and tumors that are located near sensitive organs, such as the brain or spinal cord, where the risk of radiation-induced toxicity is highest.

Brachytherapy is probably the most effective irradiation modality for reducing the risk of secondary cancer. When compared to IMRT techniques, the volume receiving low to intermediate

doses is reduced, and the theoretical risk of second cancer outside the radiation fields is reduced.

4. Justified and reasonable use of control imaging

It has become crucial to use image-guided radiotherapy. The fact that this control imaging can provide considerable doses should be kept in mind, particularly if one or more cone beam computer tomography (CBCT) procedures are carried out at each session. The majority of these imaging examinations also include volumes that are bigger than the target volumes. Therefore, we must refrain from performing additional imaging operations that are not necessary and, if necessary, take steps to lessen the dosages that this control imaging delivers. The dose associated with control imaging must also be assessed for each treatment. If this dose appears to be excessive, the technique may need to be revisited.

5. Consideration of irradiated organ

We have seen that different organs and tissues behave very differently when it comes to their susceptibility to carcinogenesis. Some, like the small intestine, appear to be particularly resistant to radio-carcinogenesis, and the likelihood of developing radiation-induced cancer at that level appears to be very low. Contrarily, the thyroid and the mammary gland are "high-risk" organs for radiation-induced malignancies, while the majority of the other organs fall somewhere in the middle.

Consideration of the irradiated organ is closely intertwined with the patient's age at the time of treatment. As younger children are seen to be more radiosensitive than adults.

6. Physical exercise

It has been hypothesized that exercise may have radio-protective effects due to molecular effects via cellular adaptations such as increased nutraceutical availability to reduce

oxidative stress, increased antioxidant activity, increased DNA repair capacity, and increased resistance to ROS/inflammatory damage. However, no human trials have been conducted to date that directly link radioprotection and exercise. The data presented suggest that aerobic and resistive exercise performed before, during, and after irradiation increases antioxidant activity and DNA repair, which is followed by decreased inflammation and DNA damage. Exercise had a positive effect on radiation at the cellular and tissue levels by restoring precursor cell and neurogenesis levels, as well as increasing bone mineral density, hematopoietic stem cell rescue, and progenitor cell counts (HSPC). Furthermore, physical training reduced radiation-induced fatigue, organ toxicity, and cognitive function impairments at the organ and system levels. More studies need to be carried out in order to confirm this hypothesis (123).

7. Regular follow-ups

This should be programmed based on the patient's tumor and treatment outcome, family history of cancer syndromes and life expectancy. Regular follow-ups increase the chances of catching a RISM at an early stage hence increasing the possibility of cure.

8. Chemo-protection

The use of radio-protective chemical agents, such as Amifostine, may also be a strategy to reduce the risk of radiation-induced secondary malignancies. These agents can protect normal tissues from radiation damage, lowering the risk of secondary malignancies (124).

CONCLUSION

In conclusion, our study sheds insight into radiotherapy's dual character as a potent tool in cancer treatment as well as a risk factor for radiation-induced secondary malignancies, a rare but serious late side effect. Our investigation has identified several risk factors, including age at radiation, sex, radiation dose, radiotherapy technique, type of radiation, site of radiation concomitant chemo-radiation, lifestyle and environmental factors, and genetic predisposition, which contribute to the development of these malignancies. By considering these factors when planning radiotherapy protocols, we can optimize long-term outcomes and minimize the incidence of this grave side effect.

Our research also suggests that screening high-risk patients can aid in the early detection and treatment of radiation-induced secondary malignancies. Surgery with safe margins is the preferred treatment approach, but when that is not feasible, chemotherapy or radiotherapy with advanced delivery techniques can be considered.

This study does have limitations, such as its retrospective design, small sample size, and diversity in patient demographics, which highlight the need for further research to explore the long-term effects of radiotherapy and strategies to mitigate the risk of radiation-induced secondary malignancies.

Overall, our study contributes to a better understanding of the risks associated with radiotherapy and provides insights into how we can minimize those risks to ensure the best possible outcomes for cancer patients. We hope our findings will inform clinical practice and guidelines in oncology, leading to improved patient care and outcomes.

ABSTRACT

Abstract

Introduction: Radiation-induced secondary malignancies (RISM) are late side effects of radiotherapy that can occur years after primary cancer treatment. The incidence of RISM is on the rise due to advances in the field of oncology, which have led to improved cancer survival rates. RISM can significantly affect patient outcomes and quality of life. The objective of this study was to identify risk factors associated with RISM development and evaluate treatment options.

Materials and methods: We conducted a retrospective and descriptive study on 3 patients who developed a RISM following treatment with radiotherapy at the Avicenne Military Hospital Oncology Department in Marrakech over a period of 9 years (2013-2022). This study relied on the analysis of medical records, including clinical observations, laboratory results, CT-scans, MRIs, scintigraphy, SPECT, and surgical biopsy with histopathological examination and immunohistochemical stain findings.

Results: The study identified 3 patients who developed a RISM with an average age at primary malignancy of 60.6 years and an average latency period of 10 years. The average age at secondary malignancy was 70.6 years, and the incidence of RISM was 0.19%. The histopathological examination and immunohistochemical staining confirmed chondrosarcoma of the scapula, squamous cell carcinoma of the base of the tongue, and osteosarcoma of the upper thigh in our three cases. Two of our patients were treated with surgery alone, and the third patient was treated with concomitant chemo-radiation due to the infeasibility of surgery due to tumor extension.

Conclusion: This study identified several risk factors associated with RISM development, including age at radiation, sex, genetic predisposition, lifestyle and environmental factors, radiotherapy techniques, type of radiation, site of radiation, dose of radiation, and concomitant chemo-radiation. Surgery with safe margins is the best treatment option for RISM, but when it is not feasible, chemotherapy and radiation can be considered. Our findings highlight the importance of careful consideration of RISM risk factors and treatment options when developing treatment plans for cancer patients who may require radiotherapy.

Résumés

Introduction : Les cancers radio-induits sont des effets secondaires tardifs de la radiothérapie qui peuvent survenir des années après le traitement du cancer primaire. L'incidence des cancers radio-induits est en hausse en raison des progrès dans le domaine de l'oncologie, qui ont conduit à une amélioration des taux de survie des patients atteints de cancer. Les cancers radio-induits peuvent avoir un impact significatif sur les résultats et la qualité de vie des patients. L'objectif de cette étude était d'identifier les facteurs de risque associés au développement du cancer radio-induits et les modalités de prise en charge.

Matériels et méthodes : Nous avons mené une étude rétrospective et descriptive sur 3 patients qui ont développés un cancer radio-induit après un traitement par radiothérapie au Service d'Oncologie de l'Hôpital Militaire Avicenne de Marrakech sur une période de 9 ans (2013-2022). Notre étude s'est appuyée sur l'analyse des dossiers médicaux, notamment les observations médicales, les résultats de laboratoire, les TDM, les IRM, la scintigraphie, le SPECT et la biopsie chirurgicale avec examen histopathologique et coloration immunohistochimique.

Résultats : L'âge moyen au moment du cancer primaire était de 60,6 ans. Le délai moyen de latence était de 10 ans. L'âge moyen au moment du cancer radio-induit était de 70,6 ans. L'incidence des cancers radio-induits était de 0,19%. Les cancer radio-induits ont été confirmés histologiquement dans les trois cas, avec un chondrosarcome de la scapula, un carcinome épidermoïde de la base de la langue et un ostéosarcome de la haut de cuisse. Deux de nos patients ont été traités par la chirurgie seule et le troisième patient a été traité par chemo-radiothérapie concomitante en raison de l'impossibilité de réaliser une intervention chirurgicale en raison de l'extension de la tumeur.

Conclusion : L'âge lors de la radiothérapie, le sexe, la prédisposition génétique, le mode de vie et les facteurs environnementaux, les techniques de radiothérapie, le type de radiation, le site de radiation, la dose de radiation et la chemo-radiothérapie concomitante sont des facteurs de risques avérés pour le développement d'un cancer radio-induits, et la meilleure option de traitement est la chirurgie avec une marge de sécurité mais lorsque cela est impossible, la chimiothérapie et la radiothérapie peuvent être envisagées.

ملخص

مقدمة: الأورام الخبيثة الثانوية الناتجة عن الإشعاع (RISM) هي آثار جانبية متأخرة للعلاج الإشعاعي يمكن أن تحدث بعد سنوات من علاج السرطان الأولي. إن معدل حدوث RISM في ارتفاع بسبب التقدم الذي عرفه مجال علم الأورام ، مما أدى إلى تحسين معدلات النجاة من السرطان. يمكن أن تؤثر RISM بشكل كبير على نتائج ونوعية حياة المرضى. كان الهدف من هذه الدراسة هو تحديد عوامل الخطر المرتبطة بتطوير RISM وتقييم خيارات العلاج.

المواد والطرق: لقد أجرينا دراسة استعادية ووصفية على 3 مرضى طوروا RISM بعد العلاج بالأشعة في مستشفى ابن سينا العسكري بمراكش على مدى 9 سنوات (2013-2022). اعتمدت دراستنا على تحليل السجلات الطبية ، بما في ذلك الملاحظات السريرية ، النتائج المختبرية ، التصوير المقطعي ، التصوير بالرنين المغناطيسي ، التصوير الومضاني ، التصوير المقطعي المحوسب ، والخزعة الجراحية مع فحص الأنسجة المرضية ونتائج البقع الكيميائية المناعية.

النتائج: يقدر متوسط العمر عند مرضانا الثلاثة في مرحلة السرطان الأولي ب60،6 سنة ومتوسط فترة الكمون 10 سنوات. كان متوسط العمر عند مرحلة الورم الخبيث الثانوي 70.6 سنة ، وكان معدل الإصابة يقدر بـ 0.19٪. أكد عن وجود الأورام الثانوية الناتجة عن الإشعاع بالفحص النسيجي المرضي والتلطيخ الكيميائي المناعي و نتج عنها الساركوما الغضروفية للكتف ، وسرطان الخلايا الحرشفية في قاعدة اللسان ، والساركوما العظمية في الفخذ العلوي عند حالاتنا الثلاث. عولج اثنان من مرضانا بالجراحة وحدها ، وعولج المريض الثالث بالعلاج الكيميائي المصاحب بسبب عدم جدوى الجراحة بسبب امتداد الورم.

الخلاصة: حددت دراستنا العديد من عوامل الخطر المرتبطة بظهور الأورام الثانوية الناتجة عن الإشعاع، بما في ذلك العمر عند الإشعاع ، الجنس ، الاستعداد الوراثي ، نمط الحياة والعوامل البيئية ، تقنيات العلاج الإشعاعي ، نوع الإشعاع ، موقع الإشعاع ، كمية الإشعاع ، وما يصاحب ذلك من علاج كيميائي. الجراحة تعد أفضل خيار لعلاج هذه الأورام الثانوية، ولكن عندما لا تكون ممكنة، يمكن استعمال العلاج الكيميائي والإشعاعي. تسلط النتائج التي توصلنا إليها الضوء على أهمية الدراسة الدقيقة لعوامل خطر الأورام الثانوية الناتجة عن الإشعاع وخيارات العلاج عند تحديد مخطط العلاج لمرضى السرطان الذين قد يحتاجون إلى علاج إشعاعي.

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قسم الطبيب

أقْسِم بِالله العَظِيم

أن أراقبَ الله في مِهْنَتِي.

وأن أصُونَ حياة الإنسان في كآفّةِ أطوَارهَا في كل الظروف والأحَوال باذلة وسْعِي في إنقاذها مِن الهَلاكِ والمرَضِ والألَم والقَلَق.

وأن أحفَظَ لِلنَاسِ كرَامَتهُم، وأسْتر عَوْرَتهُم، وأكتمَ سِرَّهُمْ.

وأن أكونَ عَلى الدوَام من وسائِل رحمة الله، باذلة رِعَايَتي الطبية للقريب والبعيد، للصالح والطالح، والصديق والعدو.

وأن أثابر على طلب العلم، أسَخِّرَه لِنَفْعِ الإِنْسَان ..لا لأذَاه.

وأن أُوَقّرَ مَن عَلَّمَني، وأُعَلّمَ مَن يَصْغرَني، وأكون أخـًا لِكُلِّ زَميلٍ في المِهنَةِ الطِّبِّيَة مُتعَاونِينَ عَلى البرِّ والتقوى.

وأن تكون حياتي مِصْدَاق إيمَاني في سِرّي وَعَلانيَتي، نَقِيَّة مِمّا يُشينهَا تجَاهَ الله وَرَسُولِهِ وَالمؤمِنين.

شهيدا أقول ما على والله

كليـــــــة الـطـب
و الصيدلة - مراكش
FACULTÉ DE MÉDECINE
ET DE PHARMACIE - MARRAKECH
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الأطروحة

قدمت ونوقشت علانية يوم **2023/06/13**

من طرف

السيدة دوركاس توبي أوكيشولا

المزدادة في 30 يونيو 1995 في يابا (نجيريا)

لنيل شهادة الدكتوراه في الطب

الكلمات الأساسية:

السرطان - العلاج الإشعاعي - الأورام الخبيثة الثانوية - عوامل الخطر - الوقاية – العلاج

اللجنة

السيدة	**غ. بيلباراكا** أستاذ في طب الأورام	**الرئيسة**
السيد	**ا. السعدي** أستاذ في طب الأورام	**المشرف**
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