Current Clinical and Medical Education

Received 10 Apl 2024 | Revised 12 Apl 2024 | Accepted 25 Apl 2024 | Published Online 20 May 2024

Published By: Vision Publisher

ISSN 2942-0792

CCME 02 (5), 106-115

Original Article

Radiotherapy and Its Associated Side Effects in Breast, Head and neck, Liver, Thyroid,Non-melanoma skin Cancer and Recent Treatment Strategies

Narjis Fahem Majhol Sachet[1], Hasanen Fahem Majhol Sajet[2], Mustafa Mohi Nouri Al-Owaidi[3], Safaa Raheem Muheisen Aljulihawi[4], Mohammed Kadhim Jiyad Al Idreis[5], Wathiq Neamah Ajeel Al-Gharibawi[6], Hussein Allawi Ibrahim AlKandali[7], Dhafer Jassim Kamel[8]

[1]Biotechnology /Biotechnology, Al-Qasim Green University, Iraq

[2]University of Kufa, College of Science, Department of Pathological Analyses, Iraq

[3]Medical Physics, Hilla University College Iraq

[4]Medical device Engineering, Hilla University College Iraq

[5]Hilla University College Iraq, Medical physics, Iraq

[6]University of Wasit Engineering, College of Science

[7]Medical Physics, Almustabal University College, Iraq

[8]University of diyala, Department of Chemistry, Iraq

Abstract:- One of the most important nonsurgical ways to control cancer is radiotherapy (RT). In recent decades, RT has made strides in both the biological and methodological domains. There are certain unsavoury side effects of radiation therapy, despite the fact that it is a groundbreaking adjuvant non-invasive method. To overcome these negative aspects of RT, research is ongoing. This article focuses on the genetic and physiological dangers that radiation therapy poses to cancer patients. We showed the progression of RT in the most common malignancies using dosage distribution as a parameter. There is evidence that radiation-induced mutations occur in patients who undergo radiation therapy. The main downsides, such as radiation resistance developing in cancer cells and subsequent malignancies, have also been covered. Infertility and the regeneration of reproductive cells as a result of radiation exposure have also been addressed. Lastly, we covered the most recent cancer treatment strategy involving RT. Without radiotherapy, cancer treatment would not be possible. On the other hand, radiosensitizers and ayurvedic radioprotectors can help us prepare for RT.

Keywords: Radiotherapy, Mutational changes, Infertility, Secondary malignancy, Cancer

Corresponding Author: Narjis Fahem Majhol Sachet †, Biotechnology /Biotechnology, Al-Qasim Green University, Iraq

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material,which is available to autho-rized users.

Introduction:

Worldwide, cancer ranks as the third most common cause of death and disability. Radiotherapy (RT) is the primary method of treating cancer, and more than 60% of cancer cases necessitate it, despite the lack of targeted pharmaceuticals. X-ray therapy or irradiation are other names for RT. The cancer cells are killed off when radiation breaks their DNA, which stops them from dividing and stops them from growing. Radiation can also impact normal cells that are around cancer cells [1]. There are a lot of adverse effects from RT, despite how popular it is. Epidemiological studies of those who survived the atomic bomb can shed light on the link between radiation exposure and cancer rates [2]. Cancers in their early stages are treated with radiation therapy.

Normal cells surrounding the tumour can be damaged by radiation, which is the main drawback of this treatment. Radiation dosages are limited for around 5% of cancer patients who are radiosensitive in order to avoid serious side effects from treatment. In radiation biology, we need to find markers of elevated radiosensitivity before we can begin treatment. Radiation tailored to each individual patient can be better found using this method [3-6]. varying types of cancer require patients to receive varying amounts of radiation. Tumour size, surgical approach, lymph node involvement, and cancer characteristics may all affect the dosage of radiation administered to a patient. This article discusses the latest radiation therapy treatments for different types of cancer, as well as the risks and benefits of these therapies. There is an immediate need for research on the potential genetic and physiological hazards of RT. Nearly half of all cancer patients respond well to radiation therapy (RT), making it an integral part of cancer care. There are more people living in developing nations, but fewer radiotherapy centres available to them, according to the Directory of Developing Countries.

Breast Cancer

Breast cancer treatment options include both external and internal beam radiation therapy. While EBRT uses short bursts of focused X-rays to target the outside of the diseased body, IBRT uses partial breast radiation with fewer adverse effects [7]. The procedure of inserting a radioactive implant close to the tumour is known as brachytherapy or internal beam radiation therapy. Breast and lymph node malignancies often require a 5-week course of radiation treatment ranging from 4500 to 5000 cGy. An extra dose of 1000–2000 Gy for a week is suggested to give it a boost. Instead of taking the whole dosage all at once, it is divided into smaller portions termed "fractions" and given over the course of a day. Radiation treatment often begins three to four weeks following surgery. Radiation therapy for breast cancer has a number of common side effects, including breast edoema, fatigue, skin irritation (mild or intense) in the treated area, discoloration or a bruised appearance, difficulties with breastfeeding, lymphedema, acute radiation dermatitis, and an extremely rare cancer called angiosarcoma.

Head and Neck Cancer

Brachytherapy and intensity-modulated radiation therapy (IMRT) are the mainstays of treatment for cancers of the head and neck. Modern three-dimensional conformal radiation therapy (3D-CRT) techniques, such as intensity-modulated radiotherapy, allow for precise control of radiation dose to a highly conformal target while sparing healthy tissues in the surrounding area. There are two varieties of brachytherapy: intracavitary, which involves localised radiation to an implant within a cavity, and interstitial, which involves radiation to an implant outside of a bodily cavity. In the early stages of head and neck cancer, it is recommended to administer a dosage of 56-70 Gy. It can be given every day for six weeks at a dose of 2 Gy per fraction. Dosage ranges from 56 to 66 Gy, depending on the radiation type. As a side effect, you can experience trouble swallowing, pain, hair loss, and teeth decay [9]. Xerostomia, bad teeth, poor oral hygiene, changed taste perception, malnutrition, bad sleep, and reduced speech function are all consequences of a late complication. Xerostomia, the irreversible loss of salivary gland function, is the consequence of a 35 Gy dosage.

Liver Cancer

The most up-to-date radiotherapy methods for treating liver cancer include external beam radiation treatment, 3D-CRT, IMRT, and SBRT. Safe and precise radiation therapy (SBRT) involves directing high radiation doses at a specific target area while avoiding normal tissues in the surrounding area. The three-dimensional tumour shape is precisely targeted by radiation beams supplied in several tiny volumes in 3D-CRT. Many side effects are also reflected in these techniques. Radiation treatment for liver cancer typically involves doses of approximately 70 Gy [10]. The risk of radiation-induced

liver disease (RILD) is 5% when the entire liver is exposed to radiation therapy doses of 30-33 Gy, but it increases to 50% with a dosage of 40 Gy (Fuss, Salter, Herman, & Thomas Jr, 2004). Feeling sick to your stomach, throwing up, gastritis, upper abdominal pain, bleeding in the stomach or duodenum, and extreme tiredness are all common adverse effects.

Non-Melanoma Skin Cancer

Broadly used treatments for non-melanoma skin cancer include EBRT, brachytherapy, and superficial radiation therapy (SRT). A total dosage of 45 Gy is delivered in 3 Gy doses of 15 fractions for 3 weeks period. Erythema and mild discom- fort is seen during treatment, but systemic side effects are rare. Late complications such as hyper- or hypopigmentation, telangiectasias, and atrophy are seen.

Thyroid Cancer

A typical dose of 60 Gy divided into 30 segments is administered during an EBRT treatment for thyroid cancer. Thyroid cells that cannot be surgically removed can be located and destroyed using radioactive iodine therapy, often known as iodine-131 or radioiodine, [11–14]. Side effects may include symptoms of a urinary tract infection, such as a swollen or painful salivary gland, vertigo, trouble sleeping, paralysis of the vocal cords, extreme tiredness, overall malaise, a feeling of a foreign body, numbness all over the body, and general malaise.

Colorectal Cancer

For colorectal cancer, EBRT is considered as an effective treatment at stage IV. The dosage ranges from 40 to 74 Gy with 1.8–2.0 Gy per fraction being administered to the colorectal patients. Possible side effects include nausea, bowel incontinence or stool leak- age, fatigue, tiredness, rectal irritation, skin irritation, bladder irritation along with burning sensation or pain while urinating, diarrhea, painful bowel movements, and blood in the stool. Besides, sexual problems such as vaginal irritation in women and erection issues in men are also encountered due to radiation therapy.

Prostate Cancer

When it comes to prostate cancer, the most popular and sensitive method for detecting lymph nodes and metastases is positron emission tomography (PET) with prostate-specific membrane antigen (PSMA)-based EBRT. Patients with prostate cancer who underwent treatment with external beam radiation [15–17] developed obstructive voiding symptoms, which significantly affected their quality of life. Initial stage prostate cancer treatment options include a radiation dosage of 70.2 Gy or an increased dosage of 79.2 Gy. Booster doses of 19.8-28.8 Gy are sometimes given following cancer surgery or in advanced stages of the disease. Ipotence, lethargy, lymphedema, rectal haemorrhage, radiation cystitis, hematochezia, diarrhoea, and radiation proctitis are some of the side effects.

Lung Cancer

In the treatment of lung cancer, two forms of external beam radiation therapy (EBRT) are utilised, namely, 3D-CRT and IMRT. According to Ming et al. (2016), the conventional dosage for lung cancer is 60 Gy administered in 4-5 portions, despite the fact that it does produce significant side effects. Radiation pneumonitis, which can develop anywhere from two weeks to six months following radiation therapy and reduce survival rates, is one of the serious side effects that can occur with a dose increase to 70 Gy. Other serious side effects include difficulty swallowing, shoulder stiffness, coughing, fever, breast or nipple soreness, and shortness of breath.

Endometrial Cancer

Widely used treatments for endometrial cancer include adjuvant vaginal brachytherapy and pelvic EBRT. Total dosage of 46 Gy can be delivered as 23 fractions for 5 days per week to treat early stage endometrial cancer. Also, doctors recommend an additional dosage of 1000– 2000 Gy as a boosting dosage for 1 week. Bowel incontinence, rectal bleeding, bladder irritation, and diarrhea are some common side effects accompanied by changes. in menstruation, vaginal itching, burning, dryness, and infertility.

Ovarian Cancer

For ovarian cancer, referring to the stage of the disease, four types of RT are carried out such as adjuvant RT at early stage, consolidative RT at advanced stage, salvage RT at recurrent disease, and palliative RT at metastatic disease [18-

21]. A total dosage of 22.5–33 Gy in 10–24 fractions for 5 weeks is administered for the abdomen region and an additional dose of 40–45 Gy delivered to the pelvis. For epithelial ovarian cancer, RT treatment includes EBRT to the entire abdominal cavity with 22–24 Gy in 22–24 fractions followed on the pelvis with 23.4–21.6 Gy in 12–13 fractions. Side effects such as radiation enterocolitis, bowel discomfort, and vaginal irritation. Risks and remedies of radiation therapy in various cancers are collected in Table 1.

Table 1 Risk and remedies of radiation therapy in various cancers

S. no.	Type of cancer	Radiation dosage (Gy)	Associated risks
1	Breast cancer	45–50	Swelling and heaviness in the breast, fatigue, irritation of the skin in the targeted area, and discoloration or a bruised appearance. Problems in breastfeeding, lymphedema, acute radiation dermatitis, and a very rare cancer called as angiosarcoma
2	Head and Neck Cancer	56–66	Trouble in swallowing, soreness, hair loss, tooth decay, xerostomia, oral mucositis, altered taste sensation, nutritional deficiency, poor sleep quality, and impaired speech function
3	Liver Cancer	70	Nausea, vomiting, gastritis, upper abdominal pain, gastric or duodenal bleeding, and fatigue
4	Non-melanoma Skin Cancer	45	Erythema, dermatitis, and atrophy
5	Thyroid Cancer	60	Swelling or pain of salivary gland, headache, vertigo, insomnia, vocal cord paralysis, fatigue, general malaise, foreign body sensation, body numbness, and urinary tract infection
6	Colorectal Cancer	40–74	Nausea, bowel incontinence or stool leakage, fatigue, tiredness, rectal irritation, skin irritation, bladder irritation along with burning sensation or pain while urinating, diarrhea, blood in stool, vaginal irritation in women, and erection issues in men are seen
7	Prostate Cancer	70.2	Radiation proctitis, rectal bleeding, diarrhea, hematochezia, radiation cystitis, impotence, fatigue, lymphedema, and erection problems
8	Lung Cancer	60	Shortness of breath, difficulty in swallowing, shoulder stiffness, cough, fever, breast or nipple soreness, and radiation pneumonitis
9	Endometrial Cancer	46	Bowel incontinence, rectal bleeding, bladder irritation, diarrhea, changes in menstruation, vaginal itching, burning, dryness, and infertility
10	Ovarian Cancer	22.5–33	Radiation cystitis, bowel discomfort, and vaginal irritation

Genetic mutations occurring after radiation therapy in cancer patients

A significant side effect of radiation therapy (RT) in cancer patients is chromosomal abnormalities. Radiotherapy for cancer patients is associated with structural chromosomal abnormalities and changes in copy number or numerical variations. Cancer develops when mutations occur in the genes that are normally responsible for cell division and cell repair and then accumulate in the genome. Doses of radiation have a direct correlation with the prevalence of chromosomal abnormalities, either increasing or decreasing it. An aberrant chromosome with two centromeres or chromosomes that have been translocated is called a dicentric chromosome, and it is an estimated risk of radiation dosage based on chromosomal aberration score [22]. Although cells with dicentric chromosomes are not stable enough to undergo recurrent mitosis, the chromosomes that have been translocated remain stable. Radiation treatment causes an equal number of dicentric chromosomes and translocations to be formed in peripheral blood of humans. Cells undergo free radical production during radiation treatment, which damages DNA, changes base pairs, and causes DNA to cross-link with itself. To put it simply, radiation's deleterious effects alter DNA repair mechanisms and introduce errors into DNA replication. According to recent research, cellular DNA mutations brought on by radiation therapy can be passed on and manifested in any cells that make it through the treatment. The radiation-induced bystander effect leads to DNA

damage, chromosomal instability, mutation, and cell death, all of which contribute to genomic instability. A variety of chromosomal abnormalities, such as aneuploidy, gene loss, and stable and unstable aberrations, can be caused by prolonged exposure to extremely low radiation dosages [23]. Aneuploidy caused by the separation of chromosomes during mitosis is the most common kind.

Recent treatment strategies in radiotherapy

Both intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) have recently become the gold standards for cancer treatment. Local radiation administration will enhance the target covering, reducing damage to the surrounding cells, according to the introduction of the IMRT technique. Compared to classical radiotherapy, modern radiation treatment is safer. Radiation treatment utilising X-rays is known as image-guided radiotherapy. This method involves scanning the tumour site such that the radiation field encompasses both the tumour site and its borderline. It provides a general notion of the cancer cells' and the surrounding tissues' dimensions, shape, and location. In patients with locally advanced esophageal cancer, intensity-modulated radiation and image-guided radiation can have beneficial side effects in addition to the previously mentioned risks [24]. To provide the best possible control while minimising damage to nearby cells, IMRT treatment variations are utilised. When treating complex conditions, such as distal esophageal cancer, IMRT is superior to 3D-CRT. This is why newer, less invasive techniques like IMRT and IGRT have emerged as the gold standard for radiation therapy. There will be significant therapeutic considerations related to intensity-modulated radiation therapy's ability to administer high dosage. This further improves the accuracy of IMRT and reduces its toxicity to adjacent tissues [25-30]. High-quality image-guided radiation treatment (IMRT) is ensured by image-guided radiotherapy (Grills et al., 2008), and IMRT combined with 3D-conjugated radiation therapy (CRT) increases target specificity and decreases the likelihood of myelopathy.

A technique called intensity-modulated radiotherapy (IMR) uses a simultaneous integrated boost to irradiate multiple tumours at various dosages while sparing healthy organs. The margins for planning target volumes have been reduced by recent technological developments, such as 4D-CT simulation and cone beam computed tomography (CBCT) [31–33].

Calculations have been found to be more accurate when IMRT and proton beam treatment (PBT) approaches are used in clinical settings [34-36]. Thanks to carbon ions, which have a higher atomic mass and can penetrate tumours more effectively than other particles, carbon-ion radiation therapy (CIRT) has emerged as a viable option for tumour treatment. This allows for a sufficient volume of radiation to reach the tumour site while reducing the dose to normal tissues around it. To perform transarterial radioembolization (TARE), microspheres sized 25-32.5 μM are loaded with high-energy radioisotope yttrium 90 (Y) beta rays and implanted into tumours. By employing microembolization, which refers to little to moderate embolisation, transarterial radioembolization reduces circulatory system damage. Stereotactic ablative radiation (SABR) improves outcomes for elderly individuals with non-small cell lung cancer (NSCLC). To maximise the amount of radiation that reaches the tumour, SABR uses radiation beams that intersect at various points on the tumour. As a result, a large amount of radiation is focused on a small area, specifically the tumour [37]. A major step forward in cancer treatment has been the use of radiation and chemotherapy together. Radiation therapy alone does not always produce the best results; it is most effective when combined with molecularly tailored medicines to target particular cancers.

The efficacy of this method and the reduction of side effects can be achieved by patient stratification. To mitigate the side effects on nearby cells, radio-opaque fiducial markers and other smart radio-therapy biomaterials (SRBs) can be inserted into tumor-bearing organs [38].

Gold or a metal alloy are examples of radio-opaque materials that can be used as markers to pinpoint the location of cancer. This method's low immunogenicity and toxicity levels are its primary selling points. Volumetric modulated arc therapy (VMAT), also known as the RapidArc approach, is another radiation method that provides a highly conformal dose distribution by means of a full rotation of about 360 degrees. When compared to IMRT and traditional radiation therapy, VMAT provides greater results with less collateral harm to nearby tissues. The improved version of IMRT is known as volumetric modulated arc treatment. While VMAT is still in its early stages as a therapeutic approach, it is already making a significant impact on patients' quality of life [39, 40].

SIDE EFFECTS AND THEIR MANAGEMENT

Anxiety, Depression, and Distress Radiation therapy is associated with an uptick in emotional problems including anxiety and depression6,7. Despite the fact that these issues usually go away when RT is finished, many patients still experience psychological side effects afterwards [41]. There is evidence that patients diagnosed with pancreatic cancer and lung cancer are at a higher risk of developing depression8. It is important to rule out radiotherapy-induced hypothyroidism and secondary vitamin B12 malabsorption as potential causes of psychiatric abnormalities, particularly in individuals with hn malignancy. Twenty percent of patients experience depression and ten percent experience anxiety, regardless of the stage of diagnosis or treatment purpose. However, there are no standardised distress screening programmes in Canada, thus underrepresentation is a concern. It is recommended by current guidelines to screen patients for distress at their initial post-treatment visit and at regular intervals thereafter [42, 43]. Validated tools for this purpose include the Patient Health Questionnaire-210, the Distress Thermometer, or the revised Edmonton Symptom Assessment System. When doing a screening, it is important to take into account the patient's psychosocial requirements and their level of anxiety of recurrence. If necessary, suitable resources should be referred to swiftly. A multidisciplinary strategy that incorporates both pharmaceutical and non-pharmacologic therapies is recommended for patients who have been diagnosed with depression.

Effects of Thoracic RT

Radioactive lung injury (rili) and radiation-induced cardiac disease (ricardi) are common side effects of thoracic RT [44]. Among the known complications of thoracic rt35 is radiation-induced lung harm in patients with lung, breast, esophageal, thymic, and hematologic cancers. Dyspnea and chronic lung fibrosis, which impact 5%-20% of patients, can have a significant impact on quality of life (36). There is an initial inflammatory phase called radiation pneumonitis that occurs between one to three months after radiation therapy (1-3 months after rt), followed by a chronic fibrotic phase called radiation fibrosis that occurs between six and twenty-four months after rt. While rili is possible in the majority of individuals undergoing thoracic RT, it may be more common in those with a history of smoking, COPD, or interstitial lung disease. Radiation recall pneumonitis is more common in older individuals and those who have undergone certain chemotherapies, immunotherapies, or targeted treatments. A condition known as "radiation recall" occurs when patients experience pneumonitis even after their radiation therapy treatments have ended. Common symptoms of radiation pneumonitis include shortness of breath, dry cough, and, in rare cases, fever [44]. Rare symptoms include rales and pleural friction rub, although a physical check may show no abnormalities at all. Because of these inconclusive results, rili should always be considered a possible diagnosis for these individuals. Despite the fact that studies can help in making the diagnosis, radiation pneumonitis is ultimately a clinical one; individuals experiencing symptoms are treated with steroids. Valvular disease, pericardial disease, coronary artery disease, cardiomyopathy, and conduction anomalies are some of the radiation-induced cardiac diseases that might appear years after RT completion. Smoking, diabetes, high blood pressure, obesity, and rt dosage are the most important traditional risk factors for cardiovascular disease, however there are others. In addition to focused symptom inquiry, survivors should see a doctor once a year and undergo scheduled screening for radiation-induced heart disease. No less pressing than the promotion of good lifestyle practices than the encouragement of a balanced diet, frequent physical activity, appropriate weight management, and the cessation of tobacco use. A baseline echocardiography should also be explored for high-risk survivors 6-12 months following RT. Finally, it is important for adults who have survived childhood cancer to be evaluated for cardiac damage and referred to a cardiologist every 5 to 10 years after radiation therapy. This is particularly true for survivors who were subjected to a 35 Gy dosage to the chest (or at least 15 Gy if they were also given anthracycline).

Effects of Pelvic RT

Radiation therapy is more commonly used to treat pelvic malignancies than other types of cancer. Some of the side effects of pelvic RT include problems with fertility, sexual dysfunction, and gastrointestinal toxicity. Mild to severe gastrointestinal problems, either temporary or permanent, following radiation therapy (rt) of a pelvic tumour are known as pelvic radiation disease (prd). Most negatively impacting patients' quality of life is prd, according to their reports [45]. Because each of the 22 possible gastrointestinal symptoms can have multiple causes, it is important to evaluate each symptom thoroughly when a patient presents with them. Up to half of patients experiencing pelvic RT report frequent symptoms such as diarrhoea, rectal bleeding, urgency, and faecal incontinence. Additional patient-related risk factors for prd include pelvic rt, diabetes, inflammatory bowel illness, low body mass index, smoking, and collagen

vascular disease45. The recommended evaluation and treatment for gastrointestinal symptoms associated with prd are summarised in Table iii. There is currently lower-certainty evidence of potential benefit for other pharmacologic and non-pharmacologic therapies, including amifostine, bile acid sequestrants, famotidine, selenium, aminosalicylates, sucralfate, corticosteroid enemas, dietary changes, glutamine, and green tea pills. As a result of a variety of factors, patients often experience sexual dysfunction following pelvic rt [46]. Up to half of male patients report erectile dysfunction five years following rt48, making it a typical late side effect. Decreased intimacy and self-esteem49 can also result from bowel and bladder disorders. As a first-line therapeutic option, phosphodiesterase type 5 inhibitors like sildenafil and tadalafil have been found to be helpful in treating erectile dysfunction associated with rt47,49,50. Dyspareunia49, decreased sexual desire, vaginal dryness, and stenosis are all symptoms associated with pelvic rt in women. There has been a correlation between the use of vaginal dilators and a decrease in self-reported vaginal stenosis, suggesting that these devices can increase vaginal suppleness and decrease fibrosis. Starting four weeks after rt, experts advise dilatation two to three times weekly (1-3 minutes) for nine to twelve months52. Pelvic physiotherapy and education from a qualified physiotherapist could make dilator use and progress tracking easier. Before beginning treatment, at 3-month intervals for the first two years following completion of treatment, and then every 6-months thereafter, patients should have their vaginal morbidity evaluated53. In cases of vaginal dryness during sexual activity, non-hormonal lubricants including water may be helpful54. If sexual issues develop during treatment, it may be necessary to refer the patient to a psychologist or sexual health specialist and consider sexual counselling before beginning treatment49,55. Patients who are thinking about getting pregnant following therapy should have their fertility checked before starting treatment. Specialists in maternal-fetal medicine, gynaecology, and reproductive endocrinology should work together56. Babies born to mothers who have undergone pelvic rt are more likely to be born prematurely, have a low birth weight, or have placental anomalies. A multidisciplinary team should continuously monitor these survivors during their pregnancy.

Conclusions

New methods for the efficient treatment of cancer have emerged as a result of scientific and technological progress. We need further research on some of the radiation therapy procedures before we can use them widely, while others are already in use. Despite the development of novel cancer treatments, radiation therapy (RT) is still an essential tool for the management and control of the majority of cancer types. Because it lessens the likelihood of surgery and the need for it, it is also an important tool for saving organs. The use of ayurvedic medications in conjunction with radiation therapy has shown to be an effective treatment method. The quality of life for cancer survivors might be adversely impacted by the substantial side effects of radiotherapy treatments. Additional comprehensive study is required to minimise rt-induced harmful consequences, even if improved radiation oncology treatments have mitigated some of the side effects. Care for cancer survivors should be provided by all physicians, including general practitioners in oncology, who should thoroughly evaluate and manage any complications due to radiation therapy.

References

1. Ash, P. (1980). The influence of radiation on fertility in man. The British Journal of Radiology, 53(628), 271–278.
2. Bae, S. H., Park, W., Choi, D. H., Nam, H., Kang, W. K., Park, Y. S., … Kim, H. C. (2011). Palliative radiotherapy in patients with a symptomatic pelvic mass of metastatic colorectal cancer. Radiation Oncology, 6(1), 52.
3. Bair, R. J., Bair, E., & Viswanathan, A. N. (2015). A radiopaque polymer hydrogel used as a fiducial marker in gynecologic-cancer patients receiving brachytherapy. Brachytherapy, 14(6), 876–880.
4. Begg, A. C., Stewart, F. A., & Vens, C. (2011). Strategies to improve radiotherapy with targeted drugs. Nature Reviews. Cancer, 11(4), 239–253.
5. Bendale, Y., Bendale, V., Birari-Gawande, P., Kadam, A., & Gund, P. (2015). Tumor regression with ayurvedic rasayana therapy in squamous cell carcinoma of lungs. Rasamruta, 7, 1–5.
6. Bjordal, K., Kaasa, S., & Mastekaasa, A. (1994). Quality of life in patients treated for head and neck cancer: A follow-up study 7 to 11 years after radiotherapy. International Journal of Radiation Oncology*

Biology* Physics, 28(4), 847–856.

7. Brierley, J. D. (2011). Update on external beam radiation therapy in thyroid cancer. The Journal of Clinical Endocrinology and Metabolism, 96(8), 2289–2295.

8. Budach, W., Hehr, T., Budach, V., Belka, C., & Dietz, K. (2006). A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer, 6(1), 28.

9. Chandra, A., Guerrero, T. M., Liu, H. H., Tucker, S. L., Liao, Z., Wang, X., … Chang, J. Y. (2005). Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiotherapy and Oncology, 77(3), 247–253.

10. Clivio, A., Fogliata, A., Franzetti-Pellanda, A., Nicolini, G., Vanetti, E., Wyttenbach, R., & Cozzi, L. (2009). Volumetric-modulated arc radiotherapy for carcinomas of the anal canal: A treatment planning comparison with fixed field IMRT. Radiotherapy and Oncology, 92(1), 118–124.

11. Cruz, F., & Bellver, J. (2014). Live birth after embryo transfer in an unresponsive thin endometrium. Gynecological Endocrinology, 30(7), 481–484.

12. Dawson, L. A., McGinn, C. J., Normolle, D., Ten Haken, R. K., Walker, S., Ensminger, W., & Lawrence, T. S. (2000). Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. Journal of Clinical Oncology, 18(11), 2210–2218.

13. Dayes, I. S., Whelan, T. J., Julian, J. A., Kuettel, M. R., Regmi, D., Okawara, G. S. Dubois, S. (2006). Cross-border referral for early breast cancer: An analysis of radiation fractionation patterns. Current Oncology, 13(4), 124.

14. Dolezel, M., Odrazka, K., Zouhar, M., Vaculikova, M., Sefrova, J., Jansa, J., … Kovarik, J. (2015). Comparing morbidity and cancer control after 3D-conformal (70/74 Gy) and intensity modulated radiotherapy (78/82 Gy) for prostate cancer. Strahlentherapie und Onkologie, 191(4), 338–346.

15. Eisbruch, A., Ten Haken, R. K., Kim, H. M., Marsh, L. H., & Ship, J. A. (1999). Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. International Journal of Radiation Oncology* Biology* Physics, 45(3), 577–587.

16. Fuss, M., Salter, B. J., Herman, T. S., & Thomas Jr., C. R. (2004). External beam radiation therapy for hepatocellular carcinoma: Potential of intensity- modulated and image-guided radiation therapy. Gastroenterology, 127(5), S206–S217.

17. Gensheimer, M. F., & Loo, B. W. (2017). Optimal radiation therapy for small cell lung cancer. Current Treatment Options in Oncology, 18(4), 21.

18. Gnoth, C., Godehardt, E., Frank-Herrmann, P., Friol, K., Tigges, J., & Freundl, G. (2005). Definition and prevalence of subfertility and infertility. Human Reproduction, 20(5), 1144–1147.

19. Grade, M., Difilippantonio, M. J., & Camps, J. (2015). Patterns of chromosomal aberrations in solid tumors. In Chromosomal instability in Cancer cells, (pp. 115–142). Cham: Springer.

20. Grover, S., Hill-Kayser, C. E., Vachani, C., Hampshire, M. K., DiLullo, G. A., & Metz, J. M. (2012). Patient reported late effects of gynecological cancer treatment. Gynecologic Oncology, 124(3), 399–403

21. Habbema, J. D. F., Eijkemans, M. J., Nargund, G., Beets, G., Leridon, H., & te Velde, E. R. (2009). The effect of in vitro fertilization on birth rates in western countries. Human Reproduction, 24(6), 1414–1419.

22. Harris, J. R., Lippman, M. E., Morrow, M., & Osborne, C. K. (2014). Diseases of the breast, 5th edition. United States: Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014. 1224p. https://www.ncbi.nlm.nih.gov/nlmcatalog/101616539.

23. Heim, R. A., Lench, N. J., & Swift, M. (1992). Heterozygous manifestations in four autosomal recessive human cancer-prone syndromes: Ataxia telangiectasia, xeroderma pigmentosum, Fanconi anemia, and

Bloom syndrome. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 284(1), 25–

24. Kanda, R. (1996). Comparison of the yields of translocations and dicentrics measured using conventional Giemsa staining and chromosome painting. International Journal of Radiation Biology, 69(6), 701–705

25. Kennedy, A., Nag, S., Salem, R., Murthy, R., McEwan, A. J., Nutting, C., … Coldwell, D. (2007). Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: A consensus panel report from the radioembolization brachytherapy oncology consortium. International Journal of Radiation Oncology* Biology* Physics, 68(1), 13–23.

26. Kim, G. J., Chandrasekaran, K., & Morgan, W. F. (2006). Mitochondrial dysfunction, persistently elevated levels of reactive oxygen species and radiation-induced genomic instability: A review. Mutagenesis, 21(6), 361–367.

27. Klein, E. A., Casey, G., & Silverman, R. (2006). Genetic susceptibility and oxidative stress in prostate cancer: Integrated model with implications for prevention. Urology, 68(6), 1145–1151.

28. Kuvar, N. A., Lambole, V. B., Shah, B. N., Shah, P. K., & Shah, D. P. (2013). A valuable medicinal plant-Crataeva nurvala. Pharma Science Monitor, 4, 3(1), 210-227.

29. Land, C. E., Tokunaga, M., Koyama, K., Soda, M., Preston, D. L., Nishimori, I., & Tokuoka, S. (2003). Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. Radiation Research, 160(6), 707–717.

30. Liapi, E., & Geschwind, J. F. H. (2010). Intra-arterial therapies for hepatocellular carcinoma: Where do we stand? Annals of Surgical Oncology, 17(5), 1234–1246.

31. Lin, J. H. (2016). Review structure-and dynamics-based computational design of anticancer drugs. Biopolymers, 105(1), 2–9.

32. Lorimore, S. A., & Wright, E. G. (2003). Radiation-induced genomic instability and bystander effects: Related inflammatory-type responses to radiation-induced stress and injury? A review. International Journal of Radiation Biology, 79(1), 15–25.

33. Malmanche, N., Maia, A., & Sunkel, C. E. (2006). The spindle assembly checkpoint: Preventing chromosome mis-segregation during mitosis and meiosis. FEBS Letters, 580(12), 2888–2895.

34. Ming, X., Feng, Y., Yang, C., Wang, W., Wang, P., & Deng, J. (2016). Radiation- induced heart disease in lung cancer radiotherapy: A dosimetric update. Medicine, 95(41), e5051.

35. Misra, B. B., & Dey, S. (2013). Biological activities of East Indian sandalwood tree, Santalum album (No. e96v1). In PeerJ PrePrints.

36. Morgan, W. F., Day, J. P., Kaplan, M. I., McGhee, E. M., & Limoli, C. L. (1996). Genomic instability induced by ionizing radiation. Radiation Research, 146(3), 247–258.

37. Nakayama, M., Okizaki, A., & Takahashi, K. (2016). A randomized controlled trial for the effectiveness of aromatherapy in decreasing salivary gland damage following radioactive iodine therapy for differentiated thyroid cancer. BioMed Research International, Volume 2016, Article ID 9509810,6 pages. http://dx.doi.org/10.1155/2016/9509810.

38. Nutting, C. M., Bedford, J. L., Cosgrove, V. P., Tait, D. M., Dearnaley, D. P., & Webb, S. (2001). A comparison of conformal and intensity-modulated techniques for oesophageal radiotherapy. Radiotherapy and Oncology, 61(2), 157–163.

39. Orth, M., Lauber, K., Niyazi, M., Friedl, A. A., Li, M., Maihöfer, C., … Belka, C. (2014). Current concepts in clinical radiation oncology. Radiation and Environmental Biophysics, 53(1), 1–29.

40. Palatty, P. L., Azmidah, A., Rao, S., Jayachander, D., Thilakchand, K. R., Rai, M. P., D'souza, P. F. (2014). Topical application of a sandal wood oil and turmeric based cream prevents radiodermatitis in head and

neck cancer patients undergoing external beam radiotherapy: A pilot study. The British Journal of Radiology, 87(1038), 20130490.

41. Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. BMJ 2018;361:k1415. 9. Kawase E, Karasawa K, Shimotsu S, et al. Estimation of anxiety and depression in patients with early stage breast cancer before and after radiation therapy. Breast Cancer 2012;19:147–52.

42. Howell D, Keshavarz H, Esplen MJ, et al. on behalf of the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer (cpac). A Pan Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress, Depression, and Anxiety in Adults with Cancer. Toronto, ON: cpac and the Canadian Association of Psychosocial Oncology; 2015.

43. Li M, Kennedy EB, Byrne N, et al. Management of depression in patients with cancer: a clinical practice guideline. J Oncol Pract 2016;12:747166–77.–56.

44. Turriziani A, Mattiucci GC, Montoro C, et al. Radiotherapy-related fatigue: incidence and predictive factors. Rays 2005;30:197–203.

45. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64:604–11.

46. Juvet LK, Thune I, Elvsaas IKO, et al. The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: a meta-analysis. Breast 2017;33: