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Mini Review

Radiation therapy and surgery in cancer management

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Introduction

Radiation therapy is devoted to management of patients with cancers and occasionally benign conditions by ionizing radiations. It can be used alone or in combination with other treatment modalities like surgery, chemotherapy, hormonal therapy and immunotherapy . Ionizing radiations were discovered in the 19th century, X-rays by Roentgen in 1895 and Mary Curie discovered radium from uranium ore in 1898. Ionizing radiation has been used in cancer therapy since 1899 and currently plays a role in the management of almost all types of cancer.[1] Clinical radiation therapy as a medical discipline began at the International Congress of Oncology in Paris in 1922 when Coutard and Hautant presented evidence that advanced laryngeal cancer could be cured without disastrous treatment' induced sequelae. By 1934 Coutard had developed a protracted fractionation scheme that remains the basis for current radiation therapy. In 1936 Paterson published results of the treatment of cancer with x-rays. The treatment of malignant tumours in many anatomic locations with brachytherapy, starting with radium needles and tubes, has increased steadily since 1910 and its therapeutic use was established in 1911 in the treatment of cervical cancer. With time, ionizing radiation became more precise, high-energy protons and electrons were available and treatment planning and delivery became more accurate and reproducible.[1, 2] Nearly 60% of all cancer patients in the United States undergo radiation therapy sometime during the course of their disease. Two methods of administering radiation exist: Teletherapy and Brachytherapy (excluding unsealed radioisotopes). Teletherapy uses an external radiation source and beam that is directed toward the tumour area. In contrast, brachytherapy uses an internal radiation source that is placed adjacent to or within the tumour itself.[3]Surgery is the oldest form of cancer therapy and in addition, surgical biopsy plays a key role in the diagnosis of most malignancies. Although the development of newer therapeutic modalities, including chemotherapy, hormonal therapy, radiation therapy, and immunotherapy, has led to decrease use of radical surgical procedures, surgery remains the only potential curative treatment for many cancer patients especially in our environment and it plays a lot of significant roles in the management of cancers which include prevention of cancer, diagnosis, staging, treatment and palliation.[3, 4]

Review of Literature: The role of surgery in cancer treatment

`Prevention:

There are numerous well-documented cases in which mild cellular abnormalities progress to invasive malignancy. When cellular abnormalities are encountered, prophylactic surgery can prevent the development of what otherwise would become a life threatening disease. Several types of cancer that can arise from cellular abnormalities and may be prevented by early prophylactic surgery includes cervical intraepithelial neoplasm (CIN), leukoplakia associated with dysplasia in the mouth, Barrett's oesophagus, cryptochidism, familial polyposis and ulcerative colitis, other indications include family history of premenopausal bilateral breast cancer in mother, sister, or both and MEN IIA[3, 4].

Diagnosis:

In many cases of malignancy, surgeons are asked to perform a biopsy to help determine a diagnosis. Because all subsequent treatment hinges on the histologic appearance of the tissue, a biopsy is an essential part of treatment planning. Common biopsy techniques includes fine needle aspiration biopsy (FNAB), Core needle biopsy (e.g. Tru-cut), and Open biopsy (Incisional and Excisional biopsies)[3, 4]

Staging:

The management of most malignancies depend on the stage of disease and certain procedures required for staging are performed by the surgeons although modern diagnostic facilities have reduced this dependency. Surgery may be required to provide information on disease stage if this will influence decisions regarding adjuvant therapies. Axillary dissection/sampling remains important in breast cancer, since axillary node status may determine whether or not a patient receives adjuvant cytotoxic chemotherapy. The surgeons require to do procedures like mediastinoscopy and mediastinotomy in lung cancer, laparotomy in ovariancancer to acquire tissue. Most often, the results of this staging it can be cytoreductive laparotomy correlate directly with length of survival[3, 4] **.**Treatment:/Surgical treatment of cancer can be divided into treatment of the primary lesion and treatment of metastatic foci. Curative resection should be attempted in patients assessed preoperatively as having no metastases and a lesion that is technically resectable with a margin of healthy surrounding tissue. The principles are 'En-bloc' dissection which involves resection of all of the involved tissues, together with any regional lymph nodes that may be at risk, without breaching any plane that may contain tumour, and cosmetic and functional considerations. Surgical procedures usually must be individualized to meet the needs of a particular patient, and the precise surgical procedure indicated may change over time as information about the nature and spread of the malignancy increases and as new therapeutic modalities are developed.[3, 4] cPalliation: Many operations are performed each year for the sole purpose of improving the patient's quality of life. Surgery is often justified in the face of incurable advanced disease, where the intention is palliative rather than to prolong survival. Indications for palliative procedures include haemorrhage, obstruction, and perforation of a hollow viscus, painful masses and extreme anxiety. For instance even in the face of metastatic disease, resection of gastrointestinal tumour – oesophageal, gastric and colorectal – provides important palliation from the effects of painful obstructive mass. In addition, complete resection of primary tumours of the CNS provides significant palliation, stenting of obstructed ureter at Cystoscopy by cannulation with a 'double-J' catheter, 'Toilet' procedure, e.g. simple mastectomy or amputation of a limb, for fungating tumours. Debulking surgery may also be useful as a palliative measure for large-volume tumours that are causing pressure symptoms, e.g. a large retroperitoneal sarcoma. Metastatic disease does not signal termination of the surgeon's involvement in the care of the cancer patients; rather it invites a new effort to provide patients with the best quality of life that surgery can offer[3, 4, 5] .

Radiation Therapy

The aim of radiation therapy is to deliver a precisely measured dose of radiation to a defined tumour volume with as minimal damage as possible to surrounding healthy tissue, resulting in eradication of tumour, a high quality of life and a prolongation of survival at competitive cost and effective palliation or prevention of symptoms of cancer, including pain alleviation, and restoring luminal patency, skeletal integrity, and organ function with minimal morbidity in a variety of clinical circumstances.[3, 6] The aim of therapy should be defined at the onset of the formulation of therapeutic strategy as curative, in which it is projected that the patient has a probability of surviving after adequate therapy; or palliation, in which there is little hope of the patient surviving for extended periods. Nevertheless symptoms that produce discomfort or affects self-sufficiency of the patient require treatment. In curative therapy a certain probability of significant side effects, even though undesirable, may be acceptable. However the same is not generally true in palliative treatment where side effects should be avoided. Nevertheless, it is necessary to remember that in the palliation of primary tumours, relatively high doses of radiation are required to control the tumour for the survival period of the patient (sometimes 75 – 80% of curative dose).[6] **Teletherapy** or 'external beam radiotherapy' (EBRT) is delivered using x-rays, gamma-rays, or electrons, and in specialised centers, neutrons, protons, or alpha particles. The choice of which is advantageous in certain settings depends on the unique physical and biological characteristics exhibited.[3]Gamma rays delivered by cobalt equipment is the oldest and simplest method of modern high-energy (megavoltage) radiation therapy, and in many centres especially in our environment, it remains the preferred technique for treatment because of its easy maintenance. It is also preferred for tumours situated in superficial areas of the body such as the extremities, breast, and head and neck. Radioactive cobalt undergoes nuclear decay, producing photons with energies of 1.17 and 1.33 million electron volts (MeV), with an average energy of 1.25 MeV. The maximum dose of these gamma rays is delivered 0.5 cm beneath the skin surface.[2, 3] Photons X-rays are produced in a linear accelerator or X-rays machines by focusing a beam of high-speed electrons onto a high-density metal target (usually tungsten). The kinetic energy transferred to a metal result in the release of photons. X-rays and gamma rays are both photon beams, differing only in the way they are produced in that gamma rays are produced from the nucleus and x-rays from the orbit. X-rays equipments for therapy are classified according to the energy of the x-rays emitted viz. Megavoltage and Orthovoltage (superficial & deep therapy) x-rays machines. Megavoltage (linear accelerators) in clinical use produces photons with a maximum energy of 4 – 25 MeV.he depth of tissue penetration is directly proportional to the mean energy of the photon beam (about one-third to one-fourth of the maximum photon energy). Megavoltage equipment deposits less energy near the skin surface than cobalt machines (skin sparing effect). The greatest energy deposition occurs at 1 – 6 cm beneath the surface depending on the energy, making theses machines ideal for treatment of tumours within deep body cavities such as the thorax, abdomen, and pelvis. Orthovoltage x-ray machines produce photons with energies of 0.1 - 0.4MeV (100 – 400KeV), lower than either cobalt or linear accelerators. These photons deposit most of their energy at or within millimetres of the skin surface (nil skin sparing effect), making Orthovoltage x-rays suitable for the treatment of superficial tumours of the skin and subcutaneous tissues. Before the development of higher energy (megavoltage) machines, Orthovoltage equipment was the mainstay of external-beam radiation therapy, and at high doses its use produced sunburn-like skin reaction and subcutaneous fibrosis.[2, 3, 4]

Electrons:

By eliminating the metal target used in linear accelerators, high-speed electrons can be used for radiation therapy. Because the dose of radiation delivered by electrons diminishes rapidly with tissue depth, treatment with electrons is desirable for tumours that are situated within a few centimetres of the skin surface or that overlie radiation sensitive normal tissues (e.g. spinal cord). The energy of the electron beam is chosen according to to the desired depth of tissue penetration. Electrons also are combined with photon irradiation to deliver a homogenous dose of radiation to a desired tissue depth. In addition, some radiation centers in developed world are using a single high-dose Intraoperative electron treatment for unresectable abdominal tumours (Intraoperative Radiotherapy IORT). Direct surgical exposure of the tumour reduces the dose of radiation delivered to normal tissues, thereby reducing the toxicity of treatment. However, special facilities, which are not

Heavy Particles:

A few specialized centers in western world use expensive cyclotrons to treat selected patients with neutrons, protons, pions, and alpha (helium nuclei) particles. Neutrons are heavy, electrically neutral particles. Neutron-induced damage is not affected by hypoxia and DNA repair processes compared to photon- or electron mediated injury.[7] Neutrons may be advantageous in the treatment of large, slow-growing tumours such as unresectable salivary gland neoplasms and well differentiated prostate carcinoma. Protons and alpha particles are positively charged nuclear particles that deliver their radiation dose at a defined tissue depth to small noninfiltrating tumours situated in highly radiation-sensitive tissues such as chordomas and uveal melanomas, which may be treated best with this modality.[3]Brachytherapy involves the placement of radioactive sources directly into a malignancy such as a tongue or prostate tumour (interstitial therapy) or into a body cavity adjacent to the tumour (intracavitary insertion) or on the surface of tumour (mould/surface brachytherapy).[6, 8] Brachytherapy is often combined with teletherapy to provide an extra 'boost' dose to accessible tumour e.g. in cancer of the cervix. This approach takes advantage of the exponential decrease in radiation dose with increasing distance from a radioactive source to deliver a high dose of radiation to the tumour site while minimizing the radiation exposure of the surrounding normal tissues.[3] Commonly used radioactive materials are chosen on the basis of specific characteristics such as half-life and photon energy. The common brachytherapy sources include Caesium^{137}, Iridium^{192}, Iodine^{125} and Gold^{198}. Nonsealed radionuclide therapy uses radioactive isotopes like ^{131}I, and ^{32}P in treatment of well differentiated thyroid cancers and polycythemia rubra Vera respectively.[6] The likelihood of tumour control is directly related to the radiation dose and inversely proportional to the number of tumour cells.[9] The major factor limiting the radiation dose is the tolerance of the normal tissues in the irradiated volume. Because radiation is delivered locally, complications depend on tumour location. For example, diarrhoea is associated with intestinal irradiation, alopecia with scalp irradiation, and odynophagia with throat or oesophageal irradiation. Treatment volume, dose distribution, and dose fractionation must be carefully controlled and monitored to deliver sufficient therapy while avoiding serious toxicity to normal tissues.[3, 9] The standard unit of radiation, replacing the rad, is the gray (Gy). One gray equals100 rad of Cgy and is the energy required to deliver 1 joule of energy to 1 kilogram of tissue. For most malignancies, the total dose used over a complete course of therapy is 30 - 50 Gy for palliation, 45 – 50 Gy for eradication of subclinical disease, and 60 – 70 Gy for elimination of clinically apparent disease.[3, 4, 6] Lower doses may be appropriate for unusually radiosensitive cancers such as leukaemia, lymphoma, and seminoma The effective dose required to achieve a desired results depends on the following factors: daily radiation dose, therapeutic goal (curative or palliative), tumour cell type and radiosensitivity, tumour size, tolerance of the surrounding normal tissues, future therapeutic plans (chemotherapy, surgical resection, or both), and the patient's general physical condition.[3, 4, 8] Conventional fractionation has been empirically derived. Typically, 180 - 200 cGy/day is given 5 times per week for 5 - 8 weeks (for a total dose of 50 – 70 Gy)[3].

Radiotherapy As An Adjuvant to Surgery

For treating a tumour bed after the removal of a bulky mass, to convert an inoperable lesion into an operable one,Where the primary or secondary lesion is inaccessible for adequate surgery,In the management of cancer recurrence following surgery, When radiotherapy has an advantage over surgery the treatment of primary or metastatic disease.

Applications of Radiotherapy [6]

Pre-operative radiotherapy. Post-operative radiotherapy,Intra-operative radiotherapy

Brachytherapy:. Intracavitary, Interstitial and Surface/mould brachytherapy.Stereotatic irradiation (Radiosurgery/Gamma knife).Intensity modulated radiation therapy (IMRT).3-Dimensional Conformal radiation therapy (CRT).The chosen modality of treatment and prescription of radiation depends on a number of factors as follows: [2, 3, 4, 9]Natural history of the tumour.Patients performance status as a measure of ability to withstand treatment. Extent of spread(Stage) of disease..Tumour biology/Histopathologic characteristics of the disease.Election or definition of the goal of therapy (cure or palliation).Available facility and expertiseIn our environment, the state –of- the art facilities are not available and current trends including the use of Stereotatic irradiation, Intraoperative radiotherapy, Intensity modulated radiation therapy (IMRT), and 3-Dimensional Conformal radiation therapy (CRT) are not available .In cancer management, radiation and surgery can be combined in many different ways. The general rationale for combining surgery and radiation is that the mechanism of failure for the two techniques is different and therefore success is cumulative and thus the combination of these treatment modalities produces better results than either used alone. Radiation rarely fails at the periphery of tumours, where cells are small in number and well vascularized. When radiation fails, it usually does so in the center of the tumour where there is a large volume of tumour cells often poorly vascularised with hypoxia. Surgery, in contrast, is limited by the required preservation of vital normal tissues adjacent to the tumour. In resectable cancers, the gross tumour can be removed, but vital normal tissues may limit the anatomic extent of the resection. When surgery fails under these circumstances, it is usually due to microscopic tumour cells left behind. It seems logical, therefore to consider combining the two techniques. [4, 9]

Pre-Operative And Post-Operative Radiotherapy: These terms are applied only in those instances where surgery and radiotherapy are used in /the same anatomical site. Pre-operative radiotherapy implies that tumour is irradiated prior to surgery and post-operative implies after surgery. [10] Pre-operative radiation has the advantage of sterilizing cells at the edges of the resection, and may prevent recurrence after surgery, and can damage the reproductive capability of the cancer cells which are likely to be disseminated or implanted in to the wound during surgical manipulation .The tumour mass may be reduced to a respectable one. Added irradiation of lymphatics and vascular channels of the contiguous normal tissue will help to arrest tumour cells and so down stages the tumour. [4, 6, 11].There are disadvantages in the use of pre-operative irradiation include delay in wound healing if doses exceed 5000cGy.If time to surgery is prolonged after preoperative irradiation, the histopathology reports become less reliable because, irradiation may change tumour biology and initial tumour anatomy. After irradiation it is no longer possible to give an accurate surgical staging so the patient for pre-op irradiation should be carefully to chose between the benefits and the cost to the patient. In some situations metastases may be truly be defined only at the time of surgery.[4, 6, 12] The mandatory waiting time to surgery after irradiation may be quite stressful and expensive for the patient and is a relative disadvantage . However properly administered irradiation will stop metastasis and waiting for surgery is not associated with tumour spread. The pre-op irradiation dose usually is moderate (4000 – 5000 cGy) and given in conventional 200-cGy fractions 5 days a week or in smaller total doses given more quickly in larger fractions (e.g. 3000 cGy in 10 fractions over 2 weeks, 300-cGy per day). If the total dose of radiation is kept small (less than or equal to 2000 cGy), then the delay between the radiation and surgery is reduced. When the dose reaches about 4000 cGy, it is valuable to delay the surgery (usually 4 – 6 weeks) to allow the normal tissues to recover from the radiation: total dose is greater than 5000 cGy, and the following surgery is often more difficult. However, with moderate doses of radiation and some time allowed between radiation and surgery, the resection can proceed without difficulty.[4,]The use of smaller doses of radiation over short periods, without surgical delay, has many advantages and is mostly intent, to improve the quality of life of the patient.[5, 14] . The target volumes are tailored to meet what is found at surgery.[4] Time can be allowed for wound healing so that the radiation will not interfere with this process. Post-operative radiotherapy is indicated where a residual tumour exist or is suspected after surgery and.the main aim is to sterilize the surgical bed. A disadvantage of such treatment is that it has no effect on seedlings deposited at time of surgery With this technique the pathology is less distorted, tumour reduction does not occur significantly, and the surgeon is not lulled into doing too small an operation. [4, 13] . If the major value of the pre-operative radiation is to prevent seeding, then large doses of radiation are not necessary. It has been reported that, seedlings can be prevented during treatment for carcinoma of the endometrium by use of intra-cavitary brachytherapy given before surgical treatment immediately before surgery. Post-operative radiation has a number of advantages as well. The subgroup of patients who may be helped by radiation can be defined accurately as a consequence of the surgical exploration and pathologic review and unnecessary irradiation to patients who are not likely to benefit can be avoided, and Surgery also may alter the biology and physiologic demands of the tumour left behind because of reduction in the vascular supply. Cells that were well oxygenated may be rendered physiologically hypoxic and more resistant to radiation. Another disadvantage in the peritoneal cavity is that the surgery causes loops of bowel to be trapped in specific positions and increases the likelihood of small intestinal damage by radiation e.g. radiation enteritis, intestinal perforation.[4, 10, 14].There is some uncertainty as to which technique is better for particular clinical circumstances although post-operative irradiation appears to be an increasingly favoured method. Both pre-operative and post-operative radiation appear to be valuable and the choice of the method, the dose of radiation, and time between radiation and surgery should be considered in terms of the goals planned and this is the basis joint consultation between relevant specialists.[12] In other words the benefit of the treatment option must outweigh the risk associated with it. At times cure is not an option, and the disease can only be palliated. In any case, the ultimate goal of any treatment either curative or palliative

Conclusion

For better treatment outcome, survival and improve quality of life in our patients, there must be greater interaction among cancer surgeons, radiation oncologists, medical oncologists, and pathologists stressing the combined modality approach in treatment. There should be close interaction between physicians and basic scientists allowing the transfer of clinically relevant biomedical advances to the bedside. There should be broad use of appropriate clinical trial to evaluate innovative or alternative treatment programs. . Treatment protocols to serve the patient best have to be collaborative and not antagonistic in the application of clinical trials and therapeutics options in radio oncology .

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