The Evolving Role of Post-Operative Radiotherapy In Cancer Management

Wafaa M. Abdel-Latif, Amani S. Guirguis, Hoda M. Abdel-Azeam and David G. Adeeb
Department of Oncology, El-Minia Faculty of Medicne

Abstract
Surgery and radiation can be combined in two fundamentally different ways: in a planned combined bimodality fashion, or a salvage fashion, in which surgery is used after irradiation fails or irradiation is used after surgery fails. In parallel with clinical experience, experimental work in radiation and tumor biology has advanced the theoretical foundations for this combination, and it is increasingly influencing clinical practice. The rationale for postoperative irradiation is based on the fact that it is possible to eliminate subclinical foci of tumor cells in the tumor bed (including lymph node metastases). By delivering higher doses to the volume of high-risk or known residual disease than can be achieved with preoperative irradiation, a greater tumor control may be obtained. For example, Vikram and Farr and Fletcher reported improved survival rates in patients with head and neck tumors treated with combined therapy in comparison with surgery alone.
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Introduction
Surgery and radiation therapy are locoregional treatment modalities for cancer management. When they are successful, they permanently eradicate the primary tumor and regional nodal metastatic disease. Locoregional control of a tumor is an obvious prerequisite for cure. Conversely, failure to achieve local control not only signifies failure to cure but also leaves the patient to face a variety of debilitating locoregional problems that ultimately may become insoluble and may be fatal if death from distant metastases or recurrent disease does not occur first. These virtues of locoregional control are self-evident; less conclusive is the potential salutary effect of effective regional treatment on the subsequent evolution of metastatic disease. The potential presence of micro-metastases complicates any evaluation of the effect of local treatment on the subsequent appearance of clinically evident metastases. [(1)]

Theoretical Basis Of Combining Surgery And Radiation Therapy:
Surgery and radiation can be combined in two fundamentally different ways: in a planned combined bimodality fashion, or a salvage fashion, in which surgery is used after irradiation fails or irradiation is used after surgery fails. In parallel with clinical experience, experimental work in radiation and tumor biology has advanced the theoretical foundations for this combination, and it is increasingly influencing clinical practice. The rationale for postoperative irradiation is based on the fact that it is possible to eliminate subclinical foci of tumor cells in the tumor bed (including lymph node metastases). By delivering higher doses to the volume of high-risk or known residual disease than can be achieved with preoperative irradiation, a greater tumor control may be obtained. For example, Vikram and Farr and Fletcher reported improved survival rates in patients with head and neck tumors treated with combined therapy in comparison with surgery alone. [(2)]

Subclinical Disease:
Locally invasive tumors, including all forms of cancer, infiltrate tissues around their primary site. Although local extension can occur in any direction, it typically follows the path of least resistance that is characteristic of different tumor types in different anatomic sites. Common pathways of local spread include those along fascial planes, muscle fibers, nerve sheaths, and periosteum. Important aspects of this spread are its microscopic character and potentially wide extent, creating a variable volume of grossly normal but tumor-bearing tissue around the primary tumor. This growth pattern is repeated at regional nodes harboring metastatic disease, if extracapsular extension

occurs there, and at sites of hematogenous metastasis. [(3)]

For certain types of cancer, prospective trials have failed to find benefit from adjuvant irradiation. For example, despite numerous studies, no conclusive evidence has been found that adjuvant preoperative radiation therapy influences the outcome of bladder carcinoma. Likewise, renal carcinoma does not seem to benefit from adjuvant irradiation.

Biologic Basis of Radiation Therapy
Ionizing radiation deposits energy as it traverses the absorbing medium through which it passes. The most important feature of the interaction of ionizing radiation with biological materials is the random and discrete nature of the energy deposition. Because these energy deposition events are discrete, it follows that although the average energy deposited in a macroscopic volume of biological material is rather modest, the distribution of this energy on a microscopic scale may be quite large. This explains why ionizing radiation is so efficient at producing biological damage.

Breast Cancer
Radiotherapy is given to the breast after conservation surgery and may be given to the chest wall after mastectomy to complete local treatment. The nodal areas, particularly supraclavicular fossa (SCF) and axilla, may also be treated in patients considered to be at higher risk of regional relapse.

Breast Conserving Surgery and Radiotherapy
Whole breast radiotherapy after wide local excision for small invasive breast cancers is necessary to maintain acceptable local recurrence rates. It has been shown to be equivalent, and an alternative, to mastectomy which can therefore be avoided. The question of whether it can be omitted in good prognostic tumors has been addressed but, even in these low-risk patients, radiotherapy has a significant role in reducing local recurrence (UK BASO II trial).

Table (1): Randomized trials comparing CS alone to CS with RT

Trial	Dates	Pts	FU (months)	Time-Point (years)	BCS Alone Local Failure	BCS & RT Local Failure	BCS Alone Death or distant failure	BCS & RT Death or distant failure
NSABP B-06	1976-1984	1137	248 (mean)	20	39%	14%	42%	35%
Uppsala-Örebr	1981-1988	381	103 (BCS alone)/ 109 (BCS & RT)	10	24%	9%	20%	10%
St. George/Royal Marsden	1981-1990	400	164	Crude	41%	20%	28%	26%
Ontario	1984-1989	799	91	Crude	35%	11%	30%	23%
Scotland	1985-1991	585	68	Crude	24%	6%	20%	13%
Milan III	1987-1989	567	109	10	15%	3%	16%	12%

GIT Cancers
Radiation therapy has recently been used more frequently in the adjuvant treatment of gastrointestinal malignancies. In rectal cancer, both randomized and non-randomized studies have demonstrated improved local control and survival with the use of adjuvant radiation. Both gastric and pancreatic cancer have a greater

propensity to distant metastases. A review of failure patterns after resection has, nonetheless, shown a high incidence of local recurrence and small prospective randomized studies have recently demonstrated a survival advantage with the use of adjuvant irradiation.

Central Nervous System Cancers

Advances in radiotherapeutic techniques over the last two decades have had a major impact in neuro-oncology. The advent of 3D conformal, stereotactic, IMRT, image-guided radiotherapy (IGRT), and proton solutions now offers unique opportunities for altering the therapeutic index in CNS tumors. Some elegant and practical examples include the avoidance of the optic apparatus during stereotactic radiosurgery (SRS) to prevent blindness, cochlear sparing with IMRT in children with medulloblastoma to spare hearing, minimizing the dose to the hypothalamic-pituitary axis to avoid endocrino-pathies, the emerging hypothesis of compartmental stem cell sparing to retain neurogenesis and hence memory, etc. The recent Quantitative estimates of Normal Tissue Effects in the Clinic (QUANTEC) analysis provides a new dataset for normal tissue tolerance, and although still limited in scope, it is substantially improved over what was available just 3 years ago for the treating physician. This should help standardize doseselection practices.

Genito-urinary Cancers

Urothelial carcinoma (UC) is the second most common cancer of the genitourinary tract. UC may occur in the upper urinary tract (renal pelvis and ureter) or lower urinary tract (bladder and urethra). Upper tract urothelial carcinoma (UTUC) accounts for just about 5% of UC. Although UTUC are infrequent, they tend to have a worse prognosis than UC of the bladder as 78% of UTUC is invasive at the time of diagnosis.

Lung Cancer

Non–Small Cell Lung Cancer

In Early-Stage NSCLC (Stage I, selected node negative Stage IIA) patients treated with surgery, postoperative radiotherapy is not recommended unless there are positive margins or upstaging to N2.

For Locally Advanced NSCLC (Stage II-III) PORT is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality, at least when using older RT techniques.

Gynecological Cancers

Endometrial Cancer

RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control. Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or vaginal brachy-therapy. External-beam doses for microscopic disease should be 45 to 50Gy. Initiate brachytherapy as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.

Soft-Tissue Sarcoma

RT can be administered either as primary, preoperative, or postoperative treatment. Total RT doses are always determined based on the tissue tolerance. Newer RT techniques such as brachytherapy, intraoperative RT (IORT), and intensity-modulated RT (IMRT) have led to the improvement of treatment outcomes in patients with STS. Brachytherapy involves the direct application of radioactive seeds into the tumor bed through catheters placed during surgery. Options include low-dose-rate (LDR) brachy-therapy, fractionated high-dose-rate (HDR) brachytherapy, or intraoperative HDR brachytherapy. LDR and HDR brachytherapy are associated with similar rates of local control. It has been suggested that HDR brachytherapy may be associated with lower incidences of severe toxicity; however, this has not been proven in randomized clinical trials. The main advantage of IMRT is its ability to more closely contour the high-dose radiation volume thereby minimizing the volume of high-dose radiation to the surrounding normal tissues. Additionally, image-guided techniques may allow for reduced target volumes, further minimizing toxicity. IORT is the delivery of radiation during surgery and it can be per-formed using different techniques such as electron beam RT or brachytherapy.

Summary and Conclusion

Radiation therapy is an important treatment modality in the fight of cancer management. Adjuvant radiation therapy plays a significant role in post-surgical local control of cancer which in turn improves disease free and overall survivals.

The concept of elective radiation therapy for subclinical regional metastatic disease as an adjuvant to definitive treatment of the primary site evolved over time. It has become generally accepted for adjuvant radiation therapy to be necessary for sterilization of subclinical foci of diseased cells (in the tumor bed including lymph node metastases) so the use of radiation therapy postsurgical resection reduces the risk of local recurrence. This combined approach has the potential to achieve high local control rates with minimal disfiguration or disruption of anatomy or function.

Adjuvant radiation therapy can be delivered either by external beam radiation (teletherapy), through radioactive material placed in the body near cancer cells (brachytherapy) or systemic radiation using radio-active substances travelling in the blood (eg. RAI).

References

1. Withers HR, Peters LJ, Taylor JM. dose-response relationship for radiation therapy of subclinical disease. Int J Radiat Oncol Biol Phys 1995;31:353-359.
2. Fletcher GH. The evolution of the basic concepts underlying the practice of radiotherapy from 1949 to 1977. Radio-logy 1978;127:3-19.
3. Fletcher GH. Implications of the density of clonogenic infestation in radiotherapy. Int J Radiat Oncol Biol Phys 1986;12:1675-1680.
4. Fletcher GH, Shukovsky LJ. The interplay of radiocurability and tolerance in the irradiation of human cancers. J Radiol Electrol Med Nucl 1975;56:383-400.
5. Suwinski R, Taylor JM, Withers HR. Rapid growth of microscopic rectal cancer as a determinant of response to pre-operative radiation therapy. Int J Radiat Oncol Biol Phys 1998;42:943-951.
6. Zagars GK, Schultheiss TE, Peters LJ. Inter-tumor heterogeneity and radiation dose-control curves. Radiother Oncol 1987; 8:353-362.
7. Fletcher GH. Irradiation of subclinical disease in the draining lymphatics. Int J Radiat Oncol Biol Phys 1984;10:939-942.
8. Withers HR, Suwinski R. Radiation dose response for subclinical metastases. Semin Radiat Oncol 1998;8:224-228.
9. Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1995;333:1456-1461.
10. O’Sullivan B, Davis A, Canadian Sarcoma Group, et al. Effect on radiotherapy field sizes in a recently completed Canadian Sarcoma Group and NCI Canada Clinical Trials Group randomized trial comparing pre-operative and post-operative radio-therapy in extremity soft tissue sarcoma [abstract 176]. Int J Radiat Oncol Biol Phys 1999;45;(Suppl):238-239.
11. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomised trial and an evaluation of secondary effects. Dis Colon Rectum 1993;36:564-572.
12. Peters LJ, Withers HR. Applying radiobiological principles to combined modality treatment of head and neck cancer—the time factor. Int J Radiat Oncol Biol Phys 1997;39:831-836.