Radiocurable Tumors and Non-Radiocurable Tumors

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Abstract: In Japan, the main technique for curing patients with malignant tumors has been surgery. However, the rapid aging of the population has necessitated a change in treatment strategy, and radiotherapy has become a powerful option. The main concern with radiation therapy is its reliability, since some tumors are radiocurable whereas others are not. Although radiosensitivity was first reported in 1906 by Bergonie and Tribondeau, clinical radiocurability is somewhat different. Leukemias and lymphomas, while exceedingly radiosensitive, are not readily radiocurable. This article discusses recent progress in radiotherapy and other complementary treatments, including malignant lymphomas of the stomach, head and neck cancer, and lung cancer, with special emphasis on treatment success and QOL.

Key words: Radiocurable tumor; Radiosensitivity; Radiotherapy; Malignant lymphoma; Head and neck cancer

Introduction

Japan currently is facing the effects of a rapidly aging population. Although it is fortunate that more and more people are living longer, this demographic change has created a number of problems as well. One problem specific to cancer treatment is that it has become more difficult to employ surgical resection as the primary treatment for malignant tumors. In addition, since more importance is being attached to the patient’s quality of life, simply saving a patient’s life is not necessarily the best option if severe limitations in subsequent daily living are apt to occur. Because of this, radiotherapy has been attracting increased attention. Radiotherapy, however, cannot be used as an alternative to surgical resection in every case because whereas some tumors are highly radiosensitive and thus responsive to radiotherapy, others are not.
Radiosensitivity

Determination of the conditions for which radiotherapy is effective has been a major focus of attention almost since radiant rays were discovered. In 1906, only 11 years after the discovery of radiation, Bergonie and Tribondeau carried out an experiment in which irradiation to the testis of mice was used to determine the sensitivity of tissue. They found that the sensitivity of cells to radiation is proportional to the degree of proliferative activity and inversely proportional to the degree of differentiation. In other words, undifferentiated cells with high mitotic capability are more radiosensitive. According to this principle, tissues rich in actively dividing cells generally show high sensitivity to radiation, whereas those with few such cells have low radiosensitivity.

More specifically, genital glands such as the testis and ovary, lymphatic tissue, fetal tissue, and fetus-like blast cell tissue are highly radiosensitive. Tissues with low radiosensitivity include adult bone, fatty tissue, muscle, and large vessels. Because the radiosensitivity of a tumor reflects the sensitivity of the tissue from which it has arisen, malignant lymphomas, which originate in lymphatic tissue, and seminomas, which originate in the testis, have high sensitivity to radiation. In contrast, osteogenic sarcomas and liposarcomas demonstrate low radiosensitivity.

Epithelial tumors, or cancers in the narrow sense, are considered to have moderate radiosensitivity. Among these tumors, undifferentiated carcinoma and small cell carcinoma have relatively high radiosensitivity, followed by squamous cell carcinoma. The radiosensitivity of adenocarcinoma is generally lower than that of other types of epithelial tumors. In light of this, head and neck cancer, esophageal cancer, uterine cervical cancer, and skin cancer, among which squamous cell carcinoma is common, seem to be good indications for radiotherapy.

However, even among squamous cell carcinomas of the esophagus, some are highly radiosensitive but others are not. As this indicates, radiosensitivity depends not only on the histologic type of the tumor but also on other factors. The oxygen concentration in the tumor and the mitotic cycle of tumor cells are two such factors. For example, in tumors accompanied with ulcers or inflammation, tumor cells are in a hypoxic state, and thus respond poorly to radiation. Therefore, attempts to raise the oxygen concentration in tumor tissue, to develop drugs that increase the radiosensitivity of hypoxic tumor tissue alone, and to synchronize the cell cycle have been attempted, although the results so far have been unsatisfactory.

On the other hand, recent studies have clarified the DNA repair process and regulatory mechanism of cell death in radiation-injured cells. From these studies, the presence of cancer-related genes affecting the radiosensitivity of cells has become apparent. *p53* is a well-known cancer-related gene, as are *Bel-2* and *Fas*. In addition, other genes, including hepatoma-derived growth factor (HDGF), have been found as a result of differences in radiosensitivity among esophageal cancers. In recent years, angiogenetic factors such as vascular endothelial growth factor (VEGF) have been attracting attention in conjunction with radiosensitivity. The involvement of many other genes has been suggested, and the microarray technique, which allows simultaneous examination of these genes, has been an aid to research. Table 1 lists the factors involved in

| Table 1 Factors Affecting Tumor Radiosensitivity |
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| 1. Histologic type |
| • High sensitivity: Malignant lymphoma, Seminoma, etc. |
| • Moderate sensitivity: Epithelial tumor (Carcinoma) |
| • Low sensitivity: Osteosarcoma, Malignant melanoma, etc. |
| 2. Oxygen concentration in tumor tissue: Radiosensitivity is low in the hypoxic state. |
| 3. Cell cycle: Radiosensitivity is high in M phase and low in S phase. |
| 4. Cancer-related genes: *p53*, *Bel-2*, *Fas*, VEGF, etc. |

M phase: Mitotic phase, S phase: DNA synthetic phase.
the radiosensitivity of tumors.

In the clinical setting, however, gene diagnosis and the diagnosis of factors other than histologic type are not always feasible, and initiation of treatment may be necessary before the results of such diagnoses are available. Therefore, radiotherapy currently tends to be indicated for tumors of a highly radiosensitive histologic type, while attempts to increase the radiosensitivity of the tumor and concurrent treatment may be necessary for epithelial tumors of moderate radiosensitivity.

Some clinical examples of radiotherapy of tumors are described below.

Heavy particle therapy, which is not influenced by factors that affect radiosensitivity (e.g., hypoxic cells), and photon beam therapy, which affords minimal injury to normal tissue, have recently become available in Japan. However, these treatments are not common, and therefore will not be discussed here.

**Malignant Lymphomas**

Because malignant lymphomas are highly radiosensitive, radiotherapy was commonly employed for them in the past. However, non-Hodgkin lymphomas, which predominate in Japan, are likely to spread throughout the entire body, and, therefore, radiotherapy alone did not yield favorable therapeutic results because of frequent recurrence in non-irradiated areas. Effective anticancer drugs for malignant lymphomas, such as Adriamycin, were developed, and combination chemotherapy regimens were improved. In addition, adjuvant agents such as G-CSF began to be used, resulting in considerable improvement in the therapeutic results of malignant lymphomas. Subsequently, malignant lymphomas, particularly non-Hodgkin lymphomas, were treated for a time by chemotherapy alone.

However, in the latter half of the 1990s, randomized controlled studies showed that short-term chemotherapy plus radiotherapy, rather than prolonged chemotherapy alone, achieved better results and was associated with fewer drug-related complications. The optimal combination of chemotherapy and radiotherapy to yield the best outcome is an important issue for the future.

Malignant lymphomas occurring in the stomach will be described briefly. The incidence of malignant lymphomas of the stomach is reported to be only about 1%, in contrast to gastric carcinomas. These lymphomas are divided into two types: mucosal-associated lymphoid tissue (MALT) lymphoma, which has lower malignancy, and usual diffuse B-cell lymphomas. Since MALT lymphoma is considered closely associated with *Helicobacter pylori*, patients with this disease are first treated by bacterial eradication using antibiotics. However, bacterial eradication is reported to be ineffective in 30% of patients with MALT lymphoma.

For cases of MALT lymphoma not amenable to bacterial eradication and those of diffuse lymphomas, gastrectomy was formerly the standard treatment, as in cases of gastric cancer. However, gastrectomy was associated with decreased quality of life mainly owing to postoperative dumping syndrome. To eliminate this drawback, treatment of malignant lymphomas of the stomach without gastrectomy was attempted through the cooperation of radiation oncologists from various institutions in Japan. More specifically, patients with MALT lymphoma were treated with radiotherapy alone when bacterial eradication was ineffective, while those with diffuse lymphomas were treated with a combination of chemotherapy and radiotherapy from the beginning, without eradication. Good therapeutic results were obtained in all 47 patients with gastric malignant lymphoma (22 with MALT lymphoma and 25 with diffuse lymphoma) without gastrectomy.

**Head and Neck Cancers**

Most cancers occurring in the head and neck region are squamous cell carcinomas, which
Often respond well to radiotherapy. However, radiotherapy in these cases may be less certain than surgical treatment.

Among laryngeal cancers, glottic cancer is clinically characterized by hoarse voice and, therefore, is often detected in stage I (T1N0M0) or II (T2N0M0). Radiotherapy has commonly been used for these cases with the aim of preserving the patient’s voice. Formerly, local control of glottic laryngeal cancer in the T2 stage involving the laryngeal ventricle was not necessarily satisfactory after radiotherapy alone, with local control obtained in 70–80% of patients. In Kurume University Hospital, cooperation between head and neck surgeons and radiation oncologists resulted in a combination treatment by which part of the tumor is resected to allow greater preservation of voice quality, followed by irradiation to the reduced tumor. As a result, tumor control was achieved in more than 90% of patients without loss of voice quality.

Radiotherapy has been indicated for other cancers in the head and neck region that previously might have been subject to extensive surgical resection, owing to consideration of possible postoperative decreases in quality of life, including functional disturbances in swallowing and phonation as well as esthetic problems. Anticancer drugs were combined with radiotherapy to ensure efficacy of treatment.

Although concomitant anticancer drug therapy has been employed in various ways, we used direct periodic administration of anticancer drugs into the tumor via catheter from the femoral artery, applying an angiographic technique. Bolus intra-arterial administration of anticancer drugs into the tumor once weekly during radiotherapy is highly effective and is associated with minimal adverse effects and complications of anticancer therapy, since simultaneous systemic administration of antidotes to the anticancer drugs is possible through the venous route. Therefore, this rapid intra-arterial infusion of anticancer drugs is feasible for aged patients who are not amenable to systemic chemotherapy because of its adverse effects. For example, this technique has achieved favorable results in elderly patients with unresectable cancer in the sphenoidal sinus involving the cranial base and in those with advanced lingual cancer for which surgical treatment was denied. These patients have been followed to date without recurrence.

In Kurume University Hospital, selective rapid intra-arterial infusion via the femoral artery in combination with radiotherapy is employed for the treatment of maxillary sinus cancer, instead of continuous intra-arterial infusion from the superficial temporal artery. Selective rapid intra-arterial procedure has yielded excellent results, with fewer complications in comparison with infusion of anticancer drugs from the superficial temporal artery. Recently, some patients with maxillary sinus cancer have been admitted to a radiology clinic rather than a otorhinolaryngology clinic. Thus, a combination of radiotherapy and administration of anticancer drugs tailored to the specific patient can achieve tumor control even in cases not responding adequately to radiotherapy alone.

Not only anticancer drugs, but also hyperthermia may improve efficacy when combined with radiotherapy. Therefore, hyperthermia is also an option for combined treatment in suitable cases in Kurume University Hospital.

**Lung Cancer**

Lung cancer (specifically cancer of bronchoalveolar origin as used in this paper) ranks first as the cause of death among Japanese men. This type of cancer is often advanced when detected and therefore associated with very poor therapeutic results. Radiotherapy of lung cancer is usually inferior to surgical treatment in terms of certainty, and lung tissue is susceptible to radiation. Therefore, radiotherapy for this disease is used predominantly in patients in whom radical surgery is impossible or in whom control of symptoms caused by metastasis is
attempted. However, progress in diagnostic imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), have enabled accurate diagnosis of the properties and extent of the tumor even when it is still small. There have also been advances in technology for concentrating radiation on the tumor, such as stereotactic radiation therapy and intensity-modulated radiation therapy (IMRT), focusing high-dose concentrated radiation on the tumor alone, with minimal injury to the lung.

The use of these latest techniques in diagnosis and treatment can achieve therapeutic efficacy equal to or better than that of surgical resection, even in patients with adenocarcinoma, which is known to have relatively low sensitivity to radiation. In the near future, the extension of these techniques is likely to offer treatment for lung cancer that maintains quality of life and eliminates the need for surgical resection.

**Conclusion**

Although various factors affect the radiosensitivity of tumors, histologic type is still an important indicator in clinical practice. In addition to tumors with a histologic type that is highly sensitive to radiation and thus responds well to radiation therapy, radiotherapy can be effective for tumors of a histologic type that has relatively low radiosensitivity and responds poorly to radiotherapy, provided that the mode of radiotherapy and type of combination therapy are carefully considered. Radiotherapy is expected to play an increasingly important role in the treatment of malignant tumors as Japan’s population continues to age.

**REFERENCES**