Current Status and Recent Advances in the Radiotherapy of Lung Cancer*

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The most effective cytoreductive agent known for treating cancer, short of the surgeon's knife, is radiotherapy; however, all too often, surgery or radiotherapy or both can markedly reduce or completely eliminate a local tumor but still not save the patient with lung cancer. An analysis of 617 patients with lung cancer who were treated with radiotherapy and surgery has provided us some explanations for the dismal results with these methods, to which Morton et al (see page 640) and Holmes (see page 643) have alluded elsewhere in this symposium.

Too often the radiotherapist may fail to appreciate the extent of the primary lesion and its likely nodal metastases and may be intimidated by the grim prognosis, so that he treats the patient with portals that are far too small and doses that are far too low to reasonably achieve more than limited palliation. For treatment with curative intent, it is important to administer the radiotherapy with adequate portals, which must include the nodal draining areas. Ordinarily, this means the mediastino-supracardiac and cervical areas are to be included, along with radiation to the site of the primary neoplasm. Overlooked almost invariably in the past has been involvement in the upper abdomen and the epigastric area. Observations at surgery and at postmortem examination show a high percentage of involvement of the upper abdominal lymph nodes in patients with lung cancer, a percentage equal to or exceeding that in the cervical and supracardiac areas. Lymphangiograms, arteriograms, and scanning with radioactive gallium help to tell us when to treat the upper abdomen. On the other hand, great care must be exercised when giving high doses to large portals, so that we do not exceed the patient's tolerance to radiation.

The problem centers on devising an optimum therapeutic regimen which produces a pattern of doses of radiation adequate to control the primary lesion and the disease in the nodes and yet does not exceed the tolerance of normal tissue. Hopefully, the treatment will not be worse than the disease and ideally should produce little, if any, adverse reactions and discomfort. One method of achieving adequate levels of radiation to large fields without complications is by proper timing of the dosage of radiation. Thus, in external radiotherapy to large fields if we spread the treatment over seven to nine weeks, instead of three to five, we can improve the "therapeutic ratio," so that patients can more effectively be treated with higher doses to large fields with minimal hematopoietic injury. Such techniques make it feasible to combine radiotherapy with adjunctive systemic chemotherapy. Studies performed weeks, months, and years after such protracted high-dose large-field radiotherapy have indicated that the hematopoietic and immune systems recover much more rapidly and completely than is the case following high-dose short courses of treatment. Thus, one promising new approach in the management of lung cancer is a relatively untechnical one that may be described as "altered radiation time-dose fractionation schemes" but is one of a series of new methods of radiotherapy being developed and studied to optimize the management of patients with lung cancer. This and several other new approaches are aimed primarily at improving "local control" in lung (and other) cancers.

Current statistics on radiotherapy indicate that about 60,000 patients with cancer die each year due to failure of local control, as opposed to those patients in whom systemic disease is the ultimate cause of death. Furthermore, failure to control local disease may be the predecessor to systemic disease and, therefore, is a fundamental step in the control of cancer. In general, the new approaches that are being used for local control are (1) radiosensitizers; (2) chemotherapeutic agents; (3) therapy using particles with high linear energy transfer and interstitial implantation; (4) hyperthermia; and (5) as mentioned previously, altered radiation time-dose fractionation schemes.

** Radio sensitizers

Radiosensitizers such as metronidazole (Flagyl) have no independent systemic chemotherapeutic effect but do selectively enhance the effect of radiation on the tumor itself. The total effective dose of radiation is lowered, and radiation-induced injury to normal tissues is minimized. (Metronidazole [Flagyl] has been employed extensively in the treatment of infections with Trichomonas and Entamoeba histolytica; it must be used carefully as a radiosensitizer.

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CHEST, 71: 5, MAY, 1977

SYMPHOSIUM ON LUNG CANCER 635
because the necessary doses approach toxic levels.)

CHEMOTHERAPY

In contrast to radiosensitizers, which merely poten-
tiate radiation, chemotherapeutic agents for treat-
ing cancer have an independent, direct, and
widespread, but less concentrated, cancricidal ef-
fect. As Armentrout has mentioned elsewhere in this
symposium (see page 838), combinations of sys-
temic chemotherapy, radiotherapy, and immu-
notherapy, with the goal of controlling systemic “mi-
crometastases” and “minimetastases,” are currently
being appraised in the management of lung cancer.
The use of multiple-drug regimen of chemother-
apy also offers the promise of enhancing radiation-in-
duced control of local disease with cell types of lung
cancer sensitive to the chemotherapeutic agents. In
this instance the direct chemotherapeutic effect may
be additive to the effect of radiation on the local
lesion, increasing the killing of tumor cells and per-
mitting reductions in the total dose of radiation in
some situations.

PARTICLE THERAPY

Techniques of Experimental Implantation

The area of first priority in research on radiation
in the national cancer program today is the program
of therapy using particles with high linear energy
transfer. In most oncologic centers, the methods
of radiotherapy available are limited to x-rays and
gamma rays. Some large centers also have particle
therapy with electrons; however, a few centers are
now evaluating particles with high linear energy
transfer, including neutrons, π-mesons, and heavy
ions, such as neon.

Why are we especially interested in neutrons
(subatomic nuclear particles), π-mesons, and heavy
ions (ionized molecules of elements with high
atomic number)? We are interested because all of
these particles are capable of introducing powerful
destructive energy to the cancer cell in a more con-
centrated, more effective form than that produced
by x-rays. These are forms of ionizing radiation
which, instead of being waves, are particulate com-
ponents and fundamental building blocks of the
atomic nucleus. In the laboratory, these particles are
found to break both strands of the nuclear DNA in
tumor cells, so that repair of the radiation-induced
injury does not occur as it does following radiation
with x-rays, which produces single-strand breaks.
Therefore, in an area where a tumor is underoxy-
genated (and large tumors frequently have hypoxic
areas), these particles can very efficiently kill tumor
cells where regular x-rays and electrons do it very
ineffectively. In addition, these particles, unlike x-
rays, kill cells with equal efficiency throughout the
entire cycle of generation: M, G1, S, and G2 the
cycle of generation refers to the reproductive cycle
of tumor cells and other cells that are actively pro-
liferating). Furthermore, some of these particles can
be placed with considerable precision in the tumor,
and, thus, spare normal transit tissues in a way not
possible with conventional x-ray therapy.

Computerized reconstructive radiography should
be very helpful in visualizing and planning surgical
treatment and radiotherapy of lung cancer. This
technique will be critically important in directing
external-beam radiation with x-rays. Also when im-
plantation of π-meson radiation is available, its use
may be monitored by this technique. Radiation with
mesons promises to be a powerful tool because when
the π-meson enters into a tumor cell, it actually
explodes like a nuclear explosion, producing particles
with very high atomic numbers; however, one of the
problems with heavy ions and π-mesons is that ordi-

narily an enormously expensive accelerator is nec-

essary to generate and deliver these radiations to the
patient. Radiologists of community hospitals, there-
fore, should participate in the national programs at
Los Alamos, NM, and Berkeley and Stanford, Calif,
for the time being, in order to offer their patients
access to this exciting treatment of the future.

Therapy with Interstitial Implantation

Radioactive 125Iodine is an implantable radioac-
tive isotope which is capable of efficient local de-
struction of cancerous masses in the chest. One of
the greatest advantages in the use of 125I as an
implant, is the fact that its radiation (actually soft
nuclear x-rays) has such a very low penetrating
ability that the patient's body itself easily shields the
operators and personnel from 125I radiation.
125Iodine can be implanted at thoracotomy and left
in place permanently. Although we do not have
extensive experience with the use of 125I, our early
results are encouraging. Dr. E. J. Beattie and his
colleagues at Sloan-Kettering Memorial Hospital in
New York have shown 125I to be more effective than
seeds of radon in the radiotherapy of lung cancer.
Furthermore, 125I has a very long half-life, meaning
that its radiation is produced over a year's time, so
that radiation-induced injury to adjacent blood ves-
sels and important structures is minimized. Spread-
ing the radiotherapy out over a very long period of
time is one way to improve the tolerance of normal
tissues over that of the tumor, the so-called "thera-
peutic ratio" in radiotherapy.

Radioactive 192Iradium, although it is also very
valuable and not difficult to shield, must be removed
in time and, thus, requires inserting “afterloaders” at thoracotomy. Iridium is better adapted to more accessible masses. With 192Ir, we have been impressed by the fact that in over 100 patients who had tumors at various sites which were persistent or recurrent after prior full-course radiotherapy, we were able to achieve 70 percent local control with therapy with radioactive implantation.

Conclusions

Thus, today we are suggesting the use of interstitial implants of radioisotopes as an interim approach to the problem of local control in tumors (1) at the time of thoracotomy to destroy nonresectable masses, and (2) in those neoplasms that are persistent after full-course radiotherapy. This approach can be widely available and relatively inexpensive. There is no question that the implantation of the source of radiation directly into the tumor will spare the transit tissues (both on entrance and exit) of unwanted radiation. Furthermore, direct visualization of the primary tumor and nodes will ensure optimal positioning of the implants.

Experience with currently available systems of implantation in controlling lesions which formerly could not be approached with curative intent has been most encouraging. Patients with lung cancer whose tumors are unresectable now may be offered definitive therapy in the form of interstitial implantation of a radioactive source at the time of surgery. This technique, combined with surgery and external-beam radiotherapy to achieve local and regional control, can make the patient a better candidate for systemic treatment with either immunotherapy or chemotherapy, or both, by ablating the local lesion. The burden of tumor cells is decreased, and the adverse impact of radiation on the hematopoietic and immune systems is diminished.

What happens when we combine external-beam radiotherapy with radioactive implantation? Measurement of the input of energy into the primary tumor and the draining lymph nodes shows that a very high cancercidal dose of radiation can be obtained. The dosage of radiation to the transit tissues is low. Therefore, to control primary and nodal disease, the ideal combination should be (1) lower doses to large fields for the high-risk nodal areas by means of external-beam radiotherapy and (2) radionuclide implantation directly into the primary tumor for local control. This combination ideally should include systemic chemotherapy or immunotherapy, or both, because radiation is a local and regional treatment and is not ordinarily considered to be systemic therapy; however, since radiotherapy is, in fact, cytoreductive therapy, it should, in the last analysis, augment systemic chemotherapy or immunotherapy.

Hyperthermia

In the laboratory, hyperthermia (for example, raising the temperature of a tumor to 43°C) results in a sixfold increase in the effects of radiation; 1,000 rads at 43°C can produce the tumor-killing effect of 6,000 rads at 37°C. Scientists are jokingly calling such combined effects “rad-hots” but seriously expect important advantages in improving tumor-killing effects and tolerance to radiation. This is another example of a primarily experimental technique, and no long-term clinical studies are yet available with radiation and hyperthermia.

Sanctuary Therapy

Sanctuary therapy is a form of treatment with radiation that offers promise of effectively treating a high-risk site of metastasis which could escape the attention of the oncologist. The therapy consists of “prophylactic” treatment with radiation at a level of 2,000 to 3,000 rads to the brain and spinal canal and sometimes the liver, kidneys, and gonads. The term, “sanctuary,” refers to the belief that these organs are sanctuaries for tumor cells, since many chemotherapeutic agents do not cross the so-called lipid barriers which are believed to exist in these organs. Such therapy is ordinarily used in cell types such as oat cell cancer, which commonly metastasizes to the brain and liver. It has been long known that patients with lung cancer who have symptoms of the central nervous system treated with radiation to the brain may have prolongation of their symptom-free survival rates for a substantial period of time; in contrast, sanctuary radiation is given prophylactically in asymptomatic patients. The final word has not been spoken on this subject, but it is another approach to therapy of lung cancer that must be studied further.

Conclusion

In this brief presentation, we have discussed some of the newer approaches to lung cancer and radiotherapy, some of them still experimental but offering exciting possibilities and some of proven practical value. The long-term results of these newer regimens of treatment are not known at the present time, but the early results appear to be promising.

Perhaps the most important single thought from the foregoing description of various new approaches to radiotherapy is the increasing importance of the team effort in employing combinations of these potentially powerful methods to significantly improve the management of lung cancer.