Radiotherapy (RT) is, with surgery, one of the two main methods for the locoregional treatment of cancer. Its modern era started in 1920, when Regaud showed that with proper fractionation it was possible to reduce the toxic effects of radiation on normal tissue without a correspondingly large loss of therapeutic effect on the tumor. This differential effect takes advantage of the strong regulatory mechanisms that exist in normal tissues. The roles of the dose per fraction (fractionation) and of the overall duration of the radiotherapy course (protraction) have recently been further elucidated (Tubiana et al. 1986b; Fowler 1984).

A second important advance was the measurement of dose distribution within the patient. The study of the dose-effect relationship for tumor control and injury to the normal surrounding tissues underlined the paramount importance of precise delivery of a cancericidal dose to the whole of the tumor, while sparing as much of the surrounding normal tissues as possible. A tumor was regarded as radioresistant if it could not be locally controlled by the maximum doses which provoked a small incidence of complications in the surrounding tissues. Hence, tumors were classified into three categories: the radio-sensitive, including lymphomas and seminomas; those of limited sensitivity, such as squamous carcinomas and adenocarcinomas; and the radioresistant, in particular sarcomas, melanomas and tumors of the gastrointestinal tract. The philosophy of accepted risks led to the concept of the optimum dose, which is that giving the highest incidence of tumor control with the lowest rate of severe complications. The numerical value of the optimum dose varies with the histologic type of the tumor and with its size, the fractionation regimen and the technique of radiotherapy.

The current renewed interest in radiotherapy is explained by three considerations: (1) combination of surgery and RT have made conservative treatment possible; (2) chemotherapy has a relatively limited effectiveness on most solid tumors; (3) improved local control of the primary tumor does not suffice to cure the patient, but is in some patients translated into improved long-term survival.
Relationship Between Local Control and Survival

The reality of the improvement has been a subject of debate. If all patients with bulky tumors which are difficult to control already have occult metastases at the time of treatment, a gain in the frequency of local control would only result in an increased incidence of death due to distant metastases. However, a sizeable proportion of relatively large tumors have not yet metastasized. For several sites, salvage treatment for local failures results in long-term survival (Suit 1982). Moreover, metastatic spread is more frequent in those patients with uncontrolled or recurrent local tumors.

There is often a discrepancy between the reduction in the incidence of local recurrences obtained with preoperative or postoperative RT and the relatively small impact on survival. This is not surprising, since local recurrence has an impact on survival only under two conditions: (1) if the patient had no distant metastases at the time of initial treatment; (2) if the recurrence initiated a metastasis before being detected and treated (Tubiana et al. 1986a). Let us take, for example, breast cancer. Postoperative RT is able to reduce the incidence of locoregional recurrence; however, an increase in survival is observed in only a small subset of patients, namely those with a tumor located in the inner quadrants and with positive axillary nodes. For tumors of the outer quadrants, the lymphatic drainage leads to an involvement of the axillary nodes and the internal mammary chain is seldom involved. For tumors of the inner quadrants, involvement of the internal mammary chain is observed in approximately one-third of the patients with metastasis-bearing axillary nodes. It is only in this last group of patients that postoperative radiotherapy improves survival. This result is easy to interpret. A breast cancer usually initiates a metastatic spread only when it has exceeded a threshold volume of a few cubic centimeters (Koscielny et al. 1984). Thus, locoregional recurrences will initiate distant metastases only when they reach this size. Axillary recurrences are easy to detect and are likely to be treated before they can initiate metastases. Conversely, internal mammary chain recurrences are not detected early and, thus, are a likely nidus for further dissemination (Tubiana et al. 1986a).

Biological Bases of Radiotherapy

The aim of curative radiotherapy is to control the tumor. A small proportion of tumor cells (ca. 0.1%) have the capacity for unlimited division; these are called stem cells. The other tumor cells are more differentiated and can undergo only a few divisions or cannot divide at all. Tumor control can be achieved only if all the stem cells have lost their proliferating ability. Cell death after irradiation is defined by the inability to proliferate. Morphologically intact cells may not be able to proliferate. The proportion of cells surviving is related to the dose delivered. Lethal radiobiological damage is inflicted at random. Moreover, the repair of non-lethal damage is terminated in less than 1 day. Therefore, during a fractionated course of irradiation the dose-response relationship for cell killing is exponential (Fletcher 1980). Consequently, a given dose per fraction kills a fixed proportion of cells, and it takes the same number of fractions to reduce a cell population from one billion ($10^9$) cells to one million ($10^6$) as it does to reduce that population from one thousand ($10^3$) to one ($10^0$).

A partial regression is generally defined as 50% reduction in tumor size. At a first approximation this corresponds to the death of 50% of the cells. If this is obtained with a dose $D_{50}$, total clinical disappearance (complete regression) of a tumor of 100 g ($10^{11}$ cells) requires that at least 999 cells out of 1000 are killed, as a lump of 100 mg is no longer detectable. This is obtained with a dose 10 times larger: 10 $D_{50}$. If all the tumor cells are stem cells, to obtain an average of less than one surviving stem cell per tumor would, for a tumor of 100 g, require a dose equal to 36 $D_{50}$. If only 0.1% of the tumor cells are clonogenic, which appears more likely, then a dose equal to 26 $D_{50}$ would suffice. Whatever the proportion of stem cells, the tumor control dose is approximately 30 times larger than that which achieves a significant partial regression and at least 3 times larger than that which achieves complete clinical remission. In these calculations no allowance is made for tumor repopulation during the course of RT; this would correspond to 4–5 $D_{50}$. For most human tumor cell lineages the $D_{50}$ varies between 2 and 2.5 Gy (Fertil and Malaise 1985).

On the basis of this dose-effect relationship it is possible to generate a theoretical curve of radiation dose against likelihood of tumor cure. At a low dose there is insufficient cell kill to cause tumor control, since only tumors with zero stem cells are cured. As the dose is raised (close to about one lethal event per cell) the probability of control increases from 25% to 75% with a relatively small dose increment.