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The Role of Local Treatment in the Cure of Cancer

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THE CONTRIBUTION of local control in the cure of cancer remains a matter of crucial importance. At diagnosis approximately 70% of patients with cancer have no detectable distant metastasis and over half of them are cured by loco-regional treatment only [1]. In western Europe and the USA [2], out of 100 patients with cancer, approximately 22% are cured by surgery, 18% by radiotherapy (alone or associated with other agents in a combination in which radiotherapy has the prominent role) and 5% by chemotherapy (alone or in combination but with the leading role to chemotherapy). Since the use of combination treatments is becoming of increasing importance these figures are tentative.

Suit [3] has stressed that one third of patients who die do so as a consequence of failure to control loco-regional disease. This is in particular the case in patients with head and neck, gynaecological, genito-urinary and gastrointestinal cancer, bone and soft tissue sarcomas, and tumours of the central nervous system [1]. Hence, one of the main potential sources of progress is to improve loco-regional control. However since approximately half the patients whose death is caused by local extension have occult metastases at the time of initial treatment, the potential benefit related to an improvement in local control amounts to only 8–10% of patients. Nevertheless about half of the progress in the cure-rate which can be expected in the next two decades, will result from advances in local treatment and the other half from advances in systemic treatment [4]. These two fields of research are not competitive but complementary.

In patients with overt or occult distant metastases, success or failure mainly depends upon the results of systemic treatment, however the role of local treatment is also important. In patients without metastases at diagnosis the cure depends upon the effectiveness of local treatment. Improved methods eradicating the primary tumour may reduce the death rate by two mechanisms—prevention of local tumour extension and reduction of distant metastases. The effect of local extension is illustrated by the results of the EORTC trial on non-small cell lung cancer in which conventional radiotherapy (RT) was compared with RT combined with daily administration of small doses of cisplatin used as a radiosensitiser. The 3-year survival rates were, respectively 2% and 16%, $P = 0.009$ [5]. In a recent meta-analysis [6] carried out on over 2000 patients with limited small cell lung cancer included in 13 trials, the long term survival was slightly but significantly higher in patients treated by RT + chemotherapy (CT) than in patients treated by CT alone (14% vs. 9%).

The second beneficial effect of securing local control is related to the reduction in the incidence of distant metastases. Local residual disease may constitute a nidus for distant dissemination [7, 8] and it has also been pointed out that the increased mitotic activity found in residual tumour clonogens may provide an opportunity for initiating the conversion of non metastatic tumour cells into metastatic clonogens [7]. It has been shown for several types of cancer (prostate [9], head and neck tumour [10], breast [8], cervix [11]) that local control reduces the incidence of distant metastases. For example the controlled clinical trial of conservative surgery for stage II breast cancer reported by Atkins *et al.* [12] shows that when the radiation dose is too low the incidence of local recurrence and distant metastases is increased. There was, however, no difference in survival for clinical stage I breast cancer treated by radical mastectomy or conservative treatment, because in these patients the probability of nodal involvement was small and therefore the dose delivered to the nodal areas did not influence survival. Several other sets of data document an association between the lack of local control of breast tumours and an increased death rate, but this association is only evidenced in series of patients who have been followed-up for long periods. For example Hayward and Caleffi [13] and Stotter *et al.* [14] found that loco-regional recurrence is correlated with an additional hazard for survival. Recently Fisher *et al.* [15] reported also that local recurrence is associated with a higher rate of distant metastases; however they claimed that local recurrence is not a cause of distant spread but only a marker for a risk already present at initial treatment. This would argue for two different groups of breast cancer: those which have metastasis almost from the outset and those with relatively late distant dissemination. However, the existence of two groups is not consistent with the data on the natural history of breast cancer which clearly show a unimodal distribution of tumours from those with the earliest to those with the latest distant dissemination [16].

Furthermore the percentage of tumours which are cured by a local treatment without systemic therapy is much greater for small than for large tumours [16]. Moreover screening and early diagnosis lead to a substantial reduction in the incidence of metastases [17]. Thus the most likely explanation is that local recurrence is a step on the path to metastatic spread. This controversy shows that many oncologists still overlook the importance of loco-regional tumour control for the long term cure of breast cancer as well as of several other types of cancer.

Therapeutic progress will come from the introduction of more effective local treatments [18] and the identification of the subset of patients who require more aggressive treatment [4].

Efforts should be made during initial patient assessment to detect distant metastases. The efficacy of post operative RT often remains a matter of debate. Indeed the subset of patients who could potentially benefit is small since two conditions need to be fulfilled. Firstly, occult metastases should be absent or small enough to be controlled by adjuvant chemotherapy and, secondly, the likelihood of local residual disease able to initiate distant metastases before being detected and treated should be high. The delineation of this subset of patients is difficult. The assessment of the probability of distant dissemination should be

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based on a knowledge of the natural history of the tumour and of the parameters which influence it. For example in breast cancer the probability of distant dissemination increases from 15% to 75% when the diameter of the tumour increases from 1.5 cm to 5.5 cm [16]. Moreover, for a breast tumour of a given size the probability of dissemination is markedly influenced by several independent prognostic factors including the number of involved lymph nodes, the histological grade and the proliferative index [19]. Several other variables have a significant impact and progress in cancer biology is likely to identify more powerful indicators related to the accumulation of molecular defects in the neoplastic cell. This example illustrates the usefulness of multivariate analyses for each type of cancer in order to select the variables which are correlated with the probability of dissemination.

Another approach is to search for the existence of residual disease after curative treatment of the primary tumour. In this respect tumour markers such as thyroglobulin in differentiated thyroid cancer [20], thyrocalcitonin in medullary thyroid cancer [21] and erythrocyte sedimentation rate in Hodgkin's disease [22] can play a crucial role in the management strategy.

It is often claimed that the inability of post-operative RT to improve survival in patients with breast cancer was demonstrated by the meta-analysis reported by Cuzick *et al.* [23]. However there were two major defects in this study: firstly, all trials were pooled together whatever the dose delivered to the chest wall and lymph nodes, whereas several studies such as the Atkin's trial [10] have shown that doses lower than 40 or 45 Gy are inadequate. Secondly, no effort was made to subdivide patients according to the characteristics of the tumours such as tumour volume or involvement of axillary nodes [19]. Adjuvant treatment modalities manifest their effectiveness in selected subgroups of patients. For example chemotherapy is not useful in patients with a low probability of distant dissemination and post operative radiotherapy is not justified when the probability of local residual tumour is low [8, 19]. It has been shown that the likelihood of the internal mammary chain involvement is much higher in patients with medial cancers than in those with outer cancers. Thus it was no surprise to find a greater impact on survival of post-operative radiotherapy in patients with medial breast cancers [8, 24, 25]. Indeed in those patients the incidence of distant metastases is reduced when the internal mammary chain is properly irradiated at a dose higher than 40 Gy. To the best of my knowledge only three studies meet these criteria, those performed at Villejuif, Stockholm and Oslo [18]. In the Villejuif study [18] the internal mammary chain was treated in some patients by surgery alone and in others by radiotherapy alone or associated with surgery; among patients with medial cancer the survival rate was significantly higher when the internal mammary chain had been treated. In the Oslo and Stockholm randomised trials the difference in survival between the patients with or without irradiation of the internal mammary chain was similar to that observed in Villejuif, but was not statistically significant. Therefore, a joint study was carried out which demonstrated a statistically significant improvement in survival in patients with involved axillary nodes [26].

This example illustrates the methodological problems which need to be overcome. The improvement in survival which can be expected from better techniques of irradiation or from post operative radiotherapy is likely to be relatively small at the level of the whole patient population, even if it is more substantial in some subsets of patients. The demonstration of the benefit therefore requires large controlled trials [4] and these need to be properly stratified with a delineation of the putative subsets of patients in whom post operative RT could improve survival. An *a posteriori* analysis, although of a lesser statistical value, may provide useful suggestions.

From the outset, the main problem with RT was that the dose which can be delivered to the tumour was limited by the risk of toxic effects in the surrounding normal tissues. Progress has been related to four main research areas: (a) the physics of radiotherapy and technical aspects of radiation delivery systems; (b) a better understanding of the radiobiological bases of radiotherapy; (c) combination of RT with surgery and (d) combination with chemotherapy.

Radiation dose distribution and treatment planning

During the past decades a huge progress has been accomplished in the techniques of RT. In external RT the introduction of high energy radiations and of electron beams has improved the dose distribution within the treated volume. Advances in the accuracy of dose assessment due to computer dosimetry has been another great leap forward because it has allowed us to optimise the beam arrangement in order to achieve a uniform dose within the tumour and to avoid overdosage to the critical normal tissues [18, 27]. Visual optimisation is now facilitated by interactive graphic workstations and by 3D display of the tumour and anatomical structures [28]. Moreover it is now possible to take into account tissue heterogeneities [29].

Computed tomography scan and modern imaging techniques have contributed to progress since the tumour can be delineated much more precisely [30]. Furthermore, it is now possible to superimpose the images provided by several methods (for example a computed tomography scan and single photon emission tomography [31]; this superimposition allows the combination of several images in a single unified data set [32].

Treatment plan verification with portal films and quality control have helped radiotherapists to avoid errors during treatment [33].

A technique of great interest for the future is conformal radiotherapy which requires a large number of fields in order to mimimise the dose to normal tissues [34]. Multileaf collimators can be used in order to adjust the size and shape of the beam at each gantry position. All these techniques can contribute to improvement in the differential dose distribution of external beam irradiation between tumour and normal tissues and thereby contribute to an increase in the rate of local tumour control. (Brachytherapy is discussed later.)

Radiobiological bases of radiotherapy

Probability of local control related to total radiation dose and dose distribution. The aim of RT is to control tumours with a low probability of serious irreversible complications in normal tissues. It has been shown for a large number of tumours that the dose causing 50% of complications is greater than that required for local control of 50% of the tumours, but the difference is relatively small, about 5–10 Gy [35].

The probability of local cure is minimal below a certain dose which represents a practical threshold. It increases progressively as the dose increases and may reach a value close to 100% for some tumours, but it is often restricted to a smaller value on account of the limit imposed on the dose by the tolerance of normal tissues. The threshold dose, and the maximum control rate clinically achievable, depends on the pathology, the extent and location of the tumour.

It is generally assumed that a tumour is controlled only if all the clonogenic cells have suffered reproductive death and are incapable of further multiplication. For example, let us consider a tumour of 100 g, containing 10^{11} cells, 1% of which are clonogenic. It contains therefore 10^9 clonogenic cells. Let us assume that the surviving fraction after each dose of 2 Gy amounts to 50%. After 30 fractions, or a total dose of 60 Gy, the proportion of surviving cells will be 10^{-9} and, on average, one surviving cell will remain per tumour. Thus according to probability distribution, there will be 37% of tumours with no surviving cells, 37% with one cell, 18% with two cells and 8% with three or more. The percentage of cured tumours is therefore 37%. If there is an average of 0.5 surviving cell per tumour the percentage of tumours without a viable surviving cell (cured tumours) is about 60%. It is 50% (the TCD 50) for a mean survival of 0.69 cell per tumour, 10% for an average of 2.3 cells per tumour and 90% for 0.1 cell per tumour (10 surviving cells per 100 tumours). This calculation shows that the dose must be increased by approximately 5 sessions of 2 Gy to increase the cure rate from 10 to 90%, assuming that all the tumours have the same radiosensitivity [35].

Similar statistical considerations make it possible to estimate the consequences of non-uniform irradiation. For example, if a dose of 60 Gy leaves on average only one surviving cell in a tumour (cure rate 37%) an underdosage to 50 Gy in one tenth of the tumour increases the number of surviving cells to four and the cure rate becomes only 2%. Inversely, an overdosage of 70 Gy in two tenths of the tumour produces only a very small increase in the cure probability, from 37 to 40% but considerably increases the risk of complications. This discussion underlines the importance of achieving homogenous dose distribution throughout the tumour and of avoiding doses which are too high for surrounding normal tissues [36].

Factors influencing radioresponsiveness. When it became possible to irradiate tumours in a satisfactory way, it became clear that many failures were due to low tumour radioresponsiveness. Clinical experience shows that the radiosensitivity of human tumours varies widely from one histological type to another. Moreover we have learned during the past decade that there are also large variations within most histological types.

Relationships between the dose and the probability of tumour control have been studied for several human tumour types. In about half of the studies the required dose increment for increasing the local control by 30% was only slightly greater than the theoretical value assuming uniform radiosensitivity in all tumours. However, in several series the required dose increment was markedly higher [35]. In this case a likely interpretation is that the tumour series analysed consist of subsets of tumours of different radiosensitivities and therefore the dose required to obtain a large proportion of controls is much higher than necessary for most of the tumours in the series [35, 36]. Identification of the radioresistant tumours would permit a significant reduction of the dose for the other patients.

The differences in tumour radiosensitivity are due to several factors.

(a) For some time it was thought that the principal factor was variation in the proportion of anoxic tumour cells or differences in the rate of reoxygenation of tumours between fractionated treatments by radiotherapy. However, while it is accepted that hypoxic cells are present to some degree in most solid tumours, most authors do not consider that their relative radioresistance is a major cause of local failure in clinical radiotherapy. This is probably due to the efficacy of reoxygenation in most human tumours [35]. In fact, the influence of anaemia on radiation response and a trend for positive results with radiosensitisers are more often observed when there is a short overall duration of radiation therapy which supports the concept that reoxygenation requires a sufficient duration of the course of radiotherapy [37].

Until now, most results with hypoxic cell radiosensitisers have been disappointing [37]. Nevertheless, efforts continue to identify the subsets of patients in whom hypoxia is a principal cause of radioresistance, to find less toxic and more effective radiosensitisers, and to assess hypoxia and monitor reoxygenation by non-invasive techniques. A few techniques have been proposed. Sensitiser-adducts can be used as markers of tissue oxygenation since the rate of sensitiser-adduct formation in tissues is governed by intra-cellular oxygen concentration.

Two markers of oxygenation have been investigated: nitroimidazoles linked with iodinated sugars [38] and fluoromisonidazoles (labeled with ^{11}F) [39].

(b) The oxygen effect, even if it exists, is not sufficient to explain all the differences observed in the clinic; other explanations must also be envisaged. The main one is related to variations in intrinsic cellular radiosensitivity. The first survival curves for mammalian cells (in the late 1950s and early 1960s) gave the erroneous impression that there were no systematic differences in radiosensitivity between various types of tumour cells. However, at that time the precision of the technique was poor; morever, radiobiologists were mostly studying the effect of relatively large doses (3–10 Gy). It was only in 1977–1978 that this concept was challenged by Barendsen and Broerse [40] for experimental tumours and at Villejuif where, in 1978, Weininger *et al.* [41], in an *in vitro* study of three human melanoma cell lines, found a significant variation in surviving fractions, from 0.39 to 0.52 after 2 Gy. It should be remembered that after 25 fractions, a small difference in radiosensitivity causes a large difference in the proportion of surviving cells. Subsequently, Fertil and Malaise [42] firmly established the role of these variations in the intrinsic radiosensitivity of human tumour cells and showed a statistically significant correlation between the *in vitro* survival of cell lines from tumours of different histologies after 2 Gy and the dose necessary to control these types of tumours in the patient. This was subsequently confirmed [35, 43]; moreover, pretreatment assays on tumour cell lines demonstrated a higher *in vitro* survival after 2 Gy in those tumours which recurred locally [44, 45]. For example, measurements were made in primary cultures derived from 72 head and neck squamous cell carcinomas. The *in vitro* survival at 2 Gy ranged from 0.11 to 0.91, with the majority of the values spanning the relatively small range of 0.21 to 0.42. The mean values from the 12 patients whose disease recurred was 0.40, whereas the remaining 60 cultures had a mean of 0.30. Hence the difference exists but it is relatively small and there is considerable overlapping [44].

Thus, intrinsic radiosensitivity plays a great role but is only one of the factors that determine curability [44, 45]. One of the limitations of clonogenic cells assay at 2 Gy is that up to 20% of tumours contain more than one population of cells with different radiosensitivities [46]; the result of the survival of 2 Gy reflects the most sensitive population, whereas the probability of cure depends upon the most resistant one. One of the main goals for the future of RT is the introduction of reliable predictive assays [47]. In the future, these should be based on a deeper

understanding of the mechanisms which govern *in vivo* tumour cell radiosensitivity. For a given radiation dose a standard amount of damage is inflicted upon DNA, with little variation between various cell types; the differences in radiosensitivity are mostly due to variations in the process of DNA repair [35, 48]. Repair of double strand break and restitution of chromosome lesions appear to be of great importance [49], moreover the half-time for the repair of these lesions (about 2 h) is similar to the half-time required for cellular recovery as measured by split-dose or low dose-rate experiments. Large tumours are liable to be heterogeneous due to the phenomenon of tumour progression [50] and, for these, the slope of the dose–effect relationship is shallower than for small ones, suggesting a greater variability of response from one tumour to another [35].

In the poorly responding large tumours besides the total number of cells and hypoxia there must be other factors involved such as the presence of radioresistant cell lines or better repair of potentially lethal damage due to a large proportion of quiescent cells [51].

(c) In effect the probability of repair appears to be influenced by cell proliferation kinetics and rapidly proliferating tumours are more radioresponsive [52]. The comparison of tumours of different histological types has shown that, on the average, tumours with a high percentage of proliferating cells and a high rate of cell loss are those which are the most radiosensitive and the most radio-curable [35, 53]. This appears to be due to impairment of DNA repair in proliferating cells. Passage through a particular stage of the cell cycle may render DNA damage irreversible and failure to repair may be due to a reduction in the time available for repair. Hence there is a competition between repair and fixation of the DNA damage. This might explain why quiescent cells are more radioresistant than cells in cycle. Several experimental data are consistent with an increased radioresistance of quiescent cells [35]. However there is conflicting evidence and these discrepancies might be attributable to differences in the technique employed to induce quiescence. Thus the direct study of tumours during their growth is of interest since the proportion of quiescent cells increases with tumour volume. Indeed experimental data show that repair of potentially lethal damage is more important in large tumours with a high proportion of quiescent cells than in small tumours [51].

Several avenues of research are being actively explored to overcome tumour radioresistance by taking into account kinetics of cell proliferation and of DNA repair, in particular altered fractionation regimens [35].

Three parameters must be considered in radiotherapy. The total dose, the dose per session and the overall treatment time. It was long suspected that the therapeutic benefit obtained with smaller fractions results from differences in the cell kill between tumour cells and cells of slowly proliferating late responding normal tissues. Due to the shape of the cell survival curve, a reduction in the dose per session causes a decrease in the efficacy of the irradiation. In our group J. Dutreix devised in 1973 a method for investigating *in vivo* the relationship between dose per fraction and early effects [54]. Subsequently, Withers *et al.* measured this isoeffect dose as a function of fractionation for late effects [55]. These quantitative data enabled a much more precise approach of what had been formerly an intuitive guess of clinicians or researchers.

In the dose region which is relevant for radiotherapy (1–3 Gy) the shape of a dose–survival curve can be characterised by the initial slope of the curve (the linear component in the linear quadratic model) and the α/β ratio. This ratio is equal to the dose for which the cell kill due to the linear component is equal to that due to the quadratic component (or bending component). The α/β ratio is much larger for acute responding normal tissues, and tumours derived from them, than for late responding tissues. The linear component is similar for acute and late responding tissues but the quadratic component β is approximately twice as great in late than in acute responding tissues [35].

Thus a reduction in the dose per fraction causes a decrease in the effect which is greater in late responding tissues than in acute responding tissues. A simple interpretation is that the capacity for repair is greater in late responding tissues in which a high proportion of cells are quiescent than in acute responding tissues in which most cells are actively dividing. Therefore when the dose is reduced the contribution to cell kill of the quadratic component decreases more rapidly in late responding tissues than in acute responding tissues. In effect, *in vivo* human and experimental investigations [54–56] showed that a 3.3 Gy dose per session is equivalent to two fractions of 1.8 Gy at 6 h intervals for acute responding tissues. Whereas 3.3 Gy is equivalent to two sessions of 2.15 Gy for late responding tissues. Thus a decrease in the dose per session below 3 Gy selectively protects the late responding tissues, which are the most critical because these are the tissues in which severe sequelae and life threatening complications may appear. This means that the therapeutic ratio is improved by smaller doses per fraction [35, 56].

These considerations have led to trials in which two fractions per day were delivered instead of one. With this hyperfractionated regimen, the early reactions and the control of the tumours are similar but the late effects are reduced when the total dose remains the same. The clinical value of hyperfractionation is that the tolerance is increased in the late responding critical tissues which normally limit the tolerated dose. Thus overall dose can be increased. For example, in an EORTC trial for oropharyngeal cancer a conventional treatment of 70 Gy in 7 weeks given at the rate of 5 × 2 Gy per week was compared with two fractions per day of 1.15 Gy, 5 days per week up to a total dose of 80.5 Gy in 7 weeks. The results which have been recently reported show that the acute reactions are more severe, but the late reactions are the same while the effect on the tumour is increased as demonstrated by a higher rate of local control [57].

Repopulation

Tumour repopulation during the course of radiotherapy plays a major role in the response of tumours. Tumour repopulation was discovered in 1966, when the acceleration of the growth rate of the surviving cells in a mouse fibrosarcoma after an irradiation was reported by Malaise and Tubiana [58, 59]. This phenomenon was confirmed and extended by Barendsen and Broerse [60]. During the past two decades several sets of clinical and experimental data demonstrated that repopulation during radiotherapy can lower the efficacy of the treatment [35, 61]. In head and neck tumours, split-course irradiations achieved a smaller percentage of local control than continuous courses. Conversely in carcinoma of the prostate, continuous irradiation and split-course radiotherapy produced similar results. It would therefore be useful to identify the tumours in which repopulation is likely to contribute to radioresistance. Pretreatment proliferative index, or potential doubling time, are currently being explored with the hope that they might be used as predictive tests [62].

In some human tumours, shortening of overall duration of

the radiotherapy course may be beneficial because it reduces tumour repopulation. This is the aim of accelerated fractionation. However, the choice of the optimal duration must also take into account repopulation in normal tissues, in particular skin and mucosa. In the regime proposed by Saunders *et al.*, treatment is given three times a day (dose per session 1.4 Gy) for 12 consecutive days without a rest period [63]. The treatment was relatively well tolerated in a series of patients with bronchial [64] and head and neck tumours. Preliminary results show an enhanced effect on the tumour, and they justified the design of a controlled study comparing conventional to accelerated regimes. However, a few severe side effects have been reported such as myelitis [65]. Moreover, it is likely that accelerated hyperfractionated irradiation is beneficial in only a few subsets of patients [66]. Several controlled clinical trials are underway which should help us to identify the tumours for which accelerated hyperfractionation confers a therapeutic advantage. In the meantime, accelerated fractionation should be used only in controlled trials.

Low dose rate irradiation: brachytherapy techniques

In the 1960s studies were undertaken to replace radium and radon seeds by radioactive isotopes such as iridium 192 wires and caesium 137. This has resulted in a major revival of interest in the use of interstitial implants and of intracavitary brachytherapy techniques which have been pioneered in a few centres, in particular at Villejuif [67, 68].

Brachytherapy has three main advantages. Firstly, its selectivity. It is possible to deliver a high dose to a small tumour, even deeply located within the body, due to the rapid decrease in the dose rate outside the limits of the target volume. Thus it is possible to treat a tumour adjacent to a critical normal tissue or a recurrence in an irradiated volume which would not tolerate external beam RT. Secondly, the short overall duration of the course of irradiation avoids repopulation. Thirdly, the low dose rate which increases the tolerance of normal tissues and has the radiobiological advantages of hyperfractionated irradiation [69]. The model built by Turesson [70] suggests that an irradiation with a dose rate equal to 0.4 Gy/h is approximately equivalent to a fractionated irradiation with 2 Gy per fraction while an irradiation delivered at a slightly higher dose rate of 0.8 Gy/h will correspond with a higher dose per fraction (approximately 3 Gy). Thus the model predicts a reduction in the late effects and a therapeutic gain for the lower dose rate. This is indeed what was observed in a recent controlled clinical trial carried out at Villejuif in which the cumulative incidence of long term complications is lower in the patients treated with the low dose rate of 0.4 Gy/h [71].

The two main disadvantages of brachytherapy are firstly the irradiation of the operator and the staff. Afterloading techniques have much reduced the dose they receive but nevertheless the patient becomes a radioactive source and their care requires caution. Secondly, the treated volume cannot be large, otherwise the radioactive source delivers a significant whole body irradiation to the patient.

Combination of RT with surgery

The dose of radiation is limited by the risk of severe irreversible lesions in surrounding normal tissues. The probability of local recurrence is not negligible for large or radioresistant tumours following the maximum tolerated doses. Surgery, in contrast, can resect gross tumours, but the excision of all the adjacent normal tissues which might be infiltrated by tumour cells is mutilating and sometimes impossible. Their association takes advantage of the two modalities: surgical resection of the tumour and irradiation of the surrounding tissues.

When after surgery no residual tumour is clinically detectable the dose required to sterilise subclinical disease is approximately 40–50 Gy [35, 72]. The diameter of the largest occult tumour cell aggregates is less than 5 mm; therefore they contain less than 10^8 cells, about 1000 times less than the tumour of 100 g taken in the previous example. Assuming that the proportion of clonogenic cells is the same, a dose equal to two thirds of the dose needed for the 100 g tumour is adequate since a cell survival of 10^{-6} is sufficient.

This combined approach is less mutilating than surgery alone and more effective than radiotherapy alone. It has given excellent results in breast, anal and head and neck tumours [72]. However, in order to reach maximum effectiveness, the margins of resection should be free from microscopic disease [73, 74]. If they are not the dose should be higher, up to 60 Gy. Moreover, the time interval between surgery and irradiation should be kept at less than 1.5 months in order to avoid repopulation [73, 75].

Combination of chemotherapy with radiotherapy

Microscopic tumour deposits can be destroyed by radiotherapy with moderate doses of the order of 45 Gy, but even at this dose level the dimensions of the fields must remain limited to avoid complications. On the other hand, chemotherapy is a systemic treatment and its toxicity, in particular on bone marrow, limits the amounts of drug which can be given.

Radiotherapy has the advantage of being far more effective. It has an important role in the treatment of large tumours, even those which are chemosensitive such as lymphomas [76]. For example, in stage III and IV Hodgkins disease, an overview suggests that the long-term survival is slightly improved when RT is delivered on bulky disease following CT [77]. In patients with small-cell lung carcinoma [76, 78], despite the administration of aggressive modern multidrug CT, a dose of about 50 Gy is required in order to reduce the local recurrence rate to below 40%. Irradiation is necessary even when the induction CT is able to achieve complete remission in most patients, emphasising the insufficiency of the criteria used to assess the presence of residual tumour. Without RT, a very high rate (approximately 80%) of loco-regional failure has been observed after so-called complete remission [76]. A recent meta-analysis has confirmed the value of the combination of RT + CT over CT alone in limited small cell lung cancer [6].

A simple calculation can illustrate the respective roles of RT and CT in the control of a tumour [76]. Let us consider again a tumour of 100 g (10^{11} cells) in which 1% of the tumour cells are clonogenic (10^9 cells) with a D_{50} equal to 2 Gy. As discussed above, the tumour control dose 37 is approximately 60 Gy in 30 fractions. If CT has reduced the number of cells by half, corresponding with a partial remission, the tissue culture dose (TCD) is 58 Gy; it is still 54 Gy if 90% of the tumour cells have been killed, corresponding with a marked regression of the tumour size under CT. It is only when CT has caused a complete remission of the tumour (residual tumour mass smaller than 100 mg) that RT given to eradicate the remaining subclinical disease can be reduced to 20 D_{50} (40 Gy). If the tumour is radioresistant (D_{50} = 3 Gy, corresponding with a cell survival of 63% after a dose of 2 Gy), the corresponding doses are 90, 87, 81 and 60 Gy, respectively. Thus for radioresistant tumours the TCD can be reduced below the dose tolerated by normal tissues

only when CT is able to produce a complete remission in most patients.

In patients with breast cancer, a comparison of the incidence of loco-regional recurrence in patients treated by surgery alone or by surgery followed by post-operative RT [73, 79–81] shows that in over 75% of the patients, the loco-regional residual disease is controlled by RT (5-year recurrence rates equal to 30% and 6%, respectively in patients without or with post-operative RT in the trial of Fisher [80]. The addition of adjuvant CT further reduces this incidence but its relative effectiveness is limited [76, 81]. In the Danish breast cancer controlled trials, the incidence of loco-regional recurrence was slightly, but not significantly, lower in the arm treated by RT plus adjuvant CT than in the arm treated by RT alone (7% vs. 12% in premenopausal, 12% vs. 17% in post-menopausal patients). In another Danish trial the local recurrence rate was significantly lower in patients treated by RT plus CMF than in those treated by CT alone (7% vs. 24% premenopausal, 5% vs. 25% in post-menopausal patients) [81].

Another advantage of combination of RT and CT is to allow conservative treatment which can avoid mutilating surgery in a large proportion of patients. For example in advanced cancer of the larynx the cure rate after RT alone is of about 50–60% due to the large size of the tumour. When RT is preceded by CT, the long term survival is equal to that produced by mutilating surgery since the recurrences are not frequent and when they occur the patients can be salvaged by surgery. Thus in a large proportion of patients the vocal cords can be spared and therefore phonation remains normal. Similarly conservative treatment of anal cancer has become possible [1].

For a large number of drugs, their administration during the RT course enhances the toxic effect. When they are administered, in order to reconcile the needs for early administration of both agents and sequential delivery, without postponing for a long time one of the two modalities, an alternating treatment schedule has been developed in which CT and RT are interdigitated [82]. This protocol avoids much of the toxicity resulting from the concurrent administration of CT and RT [83]. Furthermore, it limits the role of tumour repopulation and allows a high intensity of treatment by shortening the time interval between the various agents. This alternating regimen is supported by the results of clinical trials carried out at Villejuif. In particular, this scheme has produced in limited small-cell lung cancer a 5-year relapse-free survival rate of about 16% [76, 78]. This remarkable result, not matched by any other method, paves the way for further progress. In a controlled clinical trial Merlano *et al.* have reported that alternating RT and CT regimen yields better survival than sequential CT and RT, in patients with advanced inoperable head and neck cancers [84].

In radioresistant tumours, associations of CT and RT have yielded relatively disappointing results [85]. This is, at least in part, due to a high correlation between radioresistance and chemoresistance, hence radioresistant tumours have a high likelihood of also being chemoresistant [86]. However, some promising results have been reported in small series of patients when continuous intravenous CT is combined with RT in cancer of the anus and bladder [1]. The assessment of this technique by controlled clinical trials is justified. Another approach is to sensitise radioresistant tumours by a concomitant administration of low doses of cisplatin [87]. Some results obtained with this technique are promising [5].

FUTURE DEVELOPMENTS

Particle therapy

In order to overcome radioresistance another approach is the use of high linear energy transfer (LET) radiation (as opposed to low-LET radiations, i.e. photons and electrons) which have two theoretical advantages: firstly, a reduction of the importance of the oxygen effect. The relative radioresistance of hypoxic cells is smaller for high LET than for low-LET radiation. Secondly, with increasing LET there is a reduction in differences of radiosensitivity between cell populations, in particular, quiescent cells are less resistant [35].

Fast neutrons are used today in about 20 centres around the world. In some tumours such as those of the salivary gland and the prostate, the clinical results appear to be better than with conventional therapy. However, the physical selectivity of neutron beams is not optimal. The use of heavy particles has been advocated in order to associate the high selectivity of proton beams with a high LET [1, 35]. However, the application of these radiations requires the use of large and extremely expensive equipment. There is presently only one centre equippped, at Berkeley. Another centre is being built at Chiba in Japan. Neutron capture therapy is based on the selective uptake of a boron compound by the malignant cells. Irradiation with slow neutrons then leads to the emission of an alpha particle. Thus the cells which have absorbed atoms of boron are irradiated selectively [88]. This method has been used with encouraging results in Japan and another centre is being built in The Netherlands with the support of the European Community.

Metabolic radiotherapy

Metabolic radiotherapy was introduced half a century ago, soon after the discovery of radioisotopes by the Joliot–Curies. Its most successful use is in the treatment of differentiated thyroid cancer with radioiodine. We have treated in Villejuif a series of over 1000 patients with follow-up ranging from 8 to 30 years. Despite a relatively low radioiodine concentration in neoplastic tissues the results are nevertheless satisfactory:

—Long-term cures of patients with metastases in the lungs or bones can be achieved; however, the cure rate is much higher in patients with small metastases with diameters of less than 5 or 6 mm [20].

—The use of thyroglobulin (Tg), an effective tumour marker, has markedly improved the outcome of treatment because it helps in the early detection of metastases in conjunction with isotope scans carried out after the administration of high amounts of radioiodine (3.7 Gbq). Furthermore thyroglobulin is also useful for monitoring the effects of treatment [20].

—The combination of radioiodine with surgery (for resection of large masses) and/or beam RT (when surgery is impossible or ineffective) has been one of the keys to success [89].

These conclusions are encouraging for radioimmunotherapy, when tumour markers are available. Monoclonal antibodies (Mabs) labeled with radionuclides are used for metabolic radiotherapy in several centres [1, 90, 91]. Theoretically they have several advantages. Scintigraphy allows an accurate estimation of tumour uptake. Moreover, the Mabs do not have to be internalised to kill the cells; whereas other immunoconjugates, such as immunotoxins, only destroy the cells when they are internalised, Mabs coupled with beta emitting nuclides can destroy cells within a range of 100–1000 μm [90] and crossfire irradiation can kill cells that have failed to bind to the Mab. The main limitation is that tumour uptake is slow and tumour

concentration is often low with regard to non-specific radioactive uptake, in particular in the reticulo-endothelial system.

Radioimmunotherapy is still in its infancy. Nevertheless, a few encouraging clinical results have been reported [90–96].

In order to improve the efficacy of immunotherapy several actions should be attempted: to lower the immunogenicity of murine antibodies by their humanisation, to reduce their size and to increase their affinity. Some of these goals are now achievable through molecular engineering [4].

Combination with biological therapies

Another promising approach is to combine radiotherapy with the new biological weapons such as cytokines or inhibitors of tumour cell proliferation [97]. Encouraging results have been reported with the combination of local treatment with interferon used as a maintenance therapy, since these biological therapies are more effective on small tumour cell aggregates. However, very few data are yet available [4].

Another approach is to use inhibitors of cell proliferation in order to reduce tumour repopulation during the course of radiotherapy [98]. Agents like interferons or tamoxifen in breast cancer, have been envisaged. However a major concern is that any potential gain in slowing down repopulation might be lost if there is a concomitant reduction of radiation sensitivity due to quiescence of tumour cells. Tamoxifen is widely used in patients with breast cancer; therefore the possible radioresistance induced by tamoxifen needs to be investigated. Currently it remains safer to combine cell specific cytotoxic drugs and radiation in rapidly proliferating tumours [76, 82].

Conclusion

From the late 1940s to the late 1970s, the cure rate for cancer has practically doubled while mutilation and other sequelae caused by treatment have been considerably reduced. Clinical investgation and applied research have been the basis for these advances, which have brought about an improvement in conventional treatment modalities and a better understanding of the natural history of human cancer. However there is still ample room for improvement. Local recurrences still occur in about 30% of the patients treated by RT and in about half of these cases cause death. Their occurrence could be lowered by better dose distribution, new methods of radiotherapy, the combination of surgery and radiotherapy and the elucidation of the causes of radioresistance. In this respect RT has yet to take full advantage of the progress in molecular biology [97].

Several avenues of research are currently being explored and many are promising. Most of the recent advances have been produced by a close integration of RT with surgery and chemotherapy. This cooperation should be pursued, but one of the challenges that the radiation oncologist now faces is to take advantage of the tremendous biological progress which has been made during the past decade. Radiation oncologists have to incorporate biology into their clinical thinking.

In order to assess the value of the new strategies they will have to launch controlled clinical trials with large numbers of patients, stratified according to their clinical and biological characteristics [4, 99]. The trials carried out on 200 or 300 patients are in many cases insufficient. Besides small pilot studies, what is now required are large trials planned in order to identify the small subsets of patients who will benefit from the new therapeutic approaches. Time has come for multicentre multinational studies and prospective meta-analyses.

Radiotherapists can confidently look to the future, undoubtedly radiotherapy is and will remain at the turn of the century an effective and prominent weapon in the fight against cancer. However, RT should evolve at the same pace as modern tumour cell biology.

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Graft vs. Leukaemia Reactions in Chronic Myeloid Leukaemia

Jonathan O. Cullis, A. John Barrett and John M. Goldman

A 39-year-old female relapsed 36 months after allogeneic bone marrow transplantation for chronic myeloid leukaemia. Infusion of peripheral blood leucocytes from her bone marrow donor resulted in complete remission, and she remains leukaemia-free 18 months later. This case provides direct evidence for a 'graft vs. leukaemia' (GVL) effect contributing to the eradication of leukaemia after marrow transplantation. Existing evidence for GVL and its possible mechanisms are reviewed.
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INITIAL PRESENTATION AND MANAGEMENT

A 39-YEAR-OLD female architect first presented in November 1984 with complaints of hair loss and fatigue. A full blood count, performed by her general practitioner to exclude iron deficiency, showed a haemoglobin of 10.1 g/dl, white blood cell count of 134 × 10^9/l and platelet count of 435 × 10^9/l. The differential showed 1% promyelocytes, 12% myelocytes, 3% metamyelocytes, 67% neutrophils, 9% lymphocytes, 1% monocytes, 2% eosinophils and 5% basophils [1]. She was referred to the local haematologist.

On clinical examination, the spleen was just palpable, but there were no other abnormal findings. A bone marrow aspirate showed marked hypercellularity with granulocytic hyperplasia consistent with a diagnosis of chronic myeloid leukaemia (CML) in chronic phase. The diagnosis was confirmed by cytogenetic analysis which revealed the presence of a complex Philadelphia