MULTIMODALITY TREATMENT OF CANCER

JOHN FREDERICK FORBES

*Department of Surgery, University of Melbourne,
Royal Melbourne Hospital*

**Different and effective modalities are available for various cancers. However, early
consideration is necessary to allow optimal integration. Failure to do this may compromise the
cure potential for some tumours. The differing biology of tumours and the efficacy of various
modalities dictates specific approaches for each. The principles of multimodality therapy can be
considered together with the biological factors affecting the success and failure of each therapy
tupe and this allows a multimodality approach to be based on careful planning. For many
tumours, where effective systemic therapy exists, there are good reasons for commencing with
a multimodality approach at the outset with adjuvant chemotherapy. Practical considerations
dictate that surgeons must play a key role in the care of cancer patients. This in turn requires
that they maintain a sound knowledge of multimodality therapy for the cancers that they treat.**

DIIFFERENT effective modalities for cancer treatment
are readily available. Surgery, radiotherapy or
cytotoxic chemotherapy can each cure patients with
cancer and for specific tumours, the careful
integration of different therapy types can produce
prolonged survival or cure, and often a dramatically
improved quality of life, where one modality alone
may fail. Patients may be deprived of optimal therapy
if no consideration is given to a combined modality
approach from the outset. There are few instances —
even acute leukaemia in children may require
radiotherapy or marrow transplantation — where
certainty exists that only one therapy modality will be
required.

A combined approach can only be of value when
each modality offers clear benefit. Surgery has been
curing various cancers for centuries. Radiotherapy,
particularly since the second world war, has been
used with increasing effectiveness — particularly
with the introduction of linear accelerators, electron
therapy and lower dose neutron therapy. Cytotoxic
chemotherapy rapidly gained acceptance soon after
methotrexate was used for the treatment of
leukaemia in 1948;[1] and now effective agents are
available for use with a variety of tumours.
Integration of therapies need not be retarded
through lack of effective therapies.

Surgeons readily accept that incisional biopsy of a
melanoma, or excisional biopsy of a rectal polyp

Reprints: Dr John F. Forbes, Department of Surgery, University of
Melbourne, Royal Melbourne Hospital, 3050, Victoria.

before referral, can compromise optimal care.
Equally they must now consider that failure to count
lymph nodes in a pathology specimen, or failure to
obtain an oestrogen receptor assay, may
compromise the care of a patient with early breast
cancer. Similarly the lack of an immediate request for
para aortic or thoracic radiotherapy for a patient with
testicular teratoma without first consulting with a
medical oncologist may not only compromise
optimal care but may deprive a patient of cure of his
disease. It is no simple matter to maintain a good
knowledge of current therapies for several different
cancers. It is necessary to know what is the optimal
approach for cancers that a surgeon commonly
treats and to seek advice early if doubt exists.

Each tumour type requires a unique approach for
combined modality therapy. This is dictated by the
efficacy of different therapies, the interaction and
morbidity of each, and the unique biological
behaviour of different tumour types. For example,
patients with breast cancer do not die from local
recurrence. They die from metastatic disease which
responds readily to a variety of systemic
approaches, including various cytotoxic agents,
additive hormonal agents, or ablative hormonal
therapy. Thus adjuvant systemic therapy is logically
considered at the outset and all surgeons treating
breast cancer must be aware of this. Melanoma also
kills by metastatic disease. However, few systemic
therapies offer anything beyond short periods of
palliation. Consequently, local control and effective

local surgery is critical to optimal results. Rectal tumours contrast with both of these. Patients die of both systemic and locally recurrent disease, and it is because the latter can be extremely difficult to treat that optimal local control is vital with initial therapy. Evidence has emerged to suggest that local control may be improved by adding radiotherapy, and consequently interest has developed in the use of radiotherapy with surgery to improve local control — a combined modality approach.[2] Thus both tumour biology and the efficacy of the treatment modality will dictate treatment approaches from the outset.

An excellent example of the success of combined modality approaches is seen with Wilms' tumour. Local treatments alone produced only modest cure rates for patients with apparently localised disease: ranging from 15% two-year survival in 1930 with surgery alone, to almost 50% with improved surgery and radiotherapy by the end of the second world war. A third modality, chemotherapy was used as an adjuvant at the time of operation, and a dramatic effect was immediately seen, with two-year survivals approaching 90% by 1960. Subsequently the addition of vincristine to the first chemotherapy agent used, Actinomycin D, has resulted in the majority of patients being cured.[3] Because systemic therapy is so effective, surgery can be active. For example, resection of residual pulmonary nodules after chemotherapy may be curative.

Principles of Combined Modality Approach

Important principles dictate the selection of therapies for a combined approach. Although specific requirements vary with each tumour type, the following considerations can be helpful in planning treatment.

1. Local therapy, surgery or radiotherapy, can only treat localised disease. Neither modality will cure patients with metastases.
2. Systemic spread, even as occult metastases, requires systemic treatment (cytotoxic chemotherapy, or endocrine therapy) for adequate control or cure.
3. Surgery is a mechanical intervention — it cannot change the biology of the disease at the cellular or molecular level. Both radiotherapy and cytotoxic chemotherapy can.
4. Clinically overt metastases are usually incurable by systemic therapy (although important exceptions exist, such as metastatic teratoma, which can be cured by cis-platinum combination regimens).
5. The expectation of cure by local therapy alone for clinically localised disease is about 50%. Beyond

this, cure rates are directly proportional to the effectiveness of systemic therapies.
6. Optimal local treatment must consider both control of disease and local morbidity. If cure is not possible, regional morbidity has greater relevance. Locally recurrent disease may contribute to local morbidity, and it is not easy to balance the relative gains of surgery and radiotherapy. Effective systemic therapy can also assist local control, and must be considered when palliative treatment to reduce local control is planned.
7. Prognostic factors can be identified that allow selection of patients with early disease who have a high risk of developing (probably already having) metastatic disease. This allows adjuvant systemic therapy to be used more precisely for the groups where it is most likely to be beneficial, and allows combined modality therapy to avoid "over" or "under" treatment.

Biological Basis for Adding Systemic Therapy Early

When clinical malignancy occurs a tumour is composed of large numbers of malignant cells. A one gm mass of tumour contains approximately one billion (10^9) cells. Cytotoxic chemotherapy regimens kill by log proportions that is to say a constant percentage of cells may be killed regardless of the starting number. Even if 99% of cells (an effective programme) were killed by a course of chemotherapy, this is only a two log fraction kill: for example the tumour cell number is reduced from 10^9 to 10^7 cells. The result is that even with effective therapy, small cell volumes become increasingly more difficult to eradicate. This is a sound reason for using effective systemic therapies as early as possible in the life of the tumour.

There are other reasons for commencing systemic therapy early. Continued cell division can result in spontaneous mutations towards resistance to specific cytotoxic agents. Using conventional mutation rate ranges (10^{-3} to 10^{-7}) it can be demonstrated that a tumour cell population passes rapidly from a state of no resistance cells to a state with a high probability of resistant cells, over one-two logs of tumour growth. This change may occur in as few as three-six doublings, a very short period of time, and it occurs early in a tumour growth possibly commencing around 1000 cells.[4] This dictates that; (a) combination cytotoxic chemotherapy is likely to be better than single agents, as mutation to produce cells resistant to two drugs with different modes of action is a less likely event; (b) alternating non cross resistant regimens — perhaps alternating after one rather than several cycles — should be superior to

continued therapy with the same regimen;[5] and (c) chemotherapy should be introduced before mutation to resistance has an opportunity to occur, (this may well be perioperative or soon after operations for adjuvant chemotherapy).[4, 5] Development of concepts such as this provide sound working models for better integration of different therapy modalities, and has formed the basis of current adjuvant trials in breast cancer, using combined modalities, supported by Australian and New Zealand surgeons.

Practical Considerations in Multi Modality Therapy
1. The majority of patients cured of tumours have been cured by surgery. It is reasonable that surgeons should resist changes in treatment approaches until it is clear that real benefits — either survival gain or acceptable decrease in morbidity — will occur. It is the clear responsibility of oncologists to convey the status of current and new multidisciplinary approaches to those surgeons treating cancer patients. All clinicians want their patients to receive optimal therapies and they will seek a multidisciplinary approach where it is shown to be beneficial. It is also reasonable to expect that surgeons will endeavour to maintain an awareness of optimal therapy strategies. It would be reasonable for patients to expect this as well.
2. Some important cancers do not seem to require a team approach, but rather are the province of a single oncologist. Leukaemia and rectal carcinoma have been in this category. However, recent evidence that suggests that postoperative radiotherapy lowers local recurrence rates is now being critically examined, and there are suggestions that additional fluorouracil may produce an additive effect. It has also been claimed that fluorouracil given intravenously at the time of operation for early large bowel cancer may lower the incidence of hepatic metastases. With the increased use of mechanical staplers to avoid colostomy it may well be that a combined approach may be necessary to ensure that one morbidity (colostomy) is not traded for another (local recurrence). The surgeon dealing with colorectal carcinoma has a busy time to keep attuned to these developments.
3. Not all cancer patients can be or should be treated by the small number of oncologists available. It would be as impractical and as unnecessary as all patients with hypertension or myocardial ischemia being managed by a cardiologist. The oncologist must however have a sound knowledge of optimal therapy for each

patient with cancer and convey this readily as appropriate. Multimodality approaches require sound communication, and it is the oncologist's responsibility to provide clear direction as to when management can and should be undertaken by the general practitioner, physician or surgeon, and when it requires specialist oncologist care.
4. A single clinician must take responsibility for total patient care. For those patients who do need specialist oncology care and multimodality therapy it is far more important that the oncologist with whom they indentify has a sound knowledge of the biology of their disease and the expectations of different treatment modalities, rather than that he or she is only a skilled surgeon, radiotherapist or chemotherapist. Combined modality therapy does not obviate the need for a sound doctor patient relationship, but rather it depends on it for success.

UNIQUE FEATURES OF DIFFERENT MODALITIES JUSTIFYING A COMBINED APPROACH

The therapeutic aims of different modalities are summarised in Table 1. When the expectations and limitations of each modality are considered, the reasons for failure become apparent and these, together with the mechanisms of interaction of each modality, justify careful planning of combined regimens.

Surgery

Operative intervention cannot alter the biology of the tumour. Surgery will fail if the tumour has spread

TABLE 1
Aims of different modalities

(a) "Curable" local disease (for example T1NoMo Breast Cancer)*	
Modality	Aims
Surgery alone	1. Tumour Removal — "cure"
	2. Minimal morbidity
Radiotherapy alone	1. Tumour removal — "cure"
	2. Minimal morbidity
Surgery plus radiotherapy	1. Equivalent tumour removal with *less* morbidity

(b) "Curable" local disease with occult spread (adjuvant therapy)	
Surgery	1. Local tumour removal
	2. Minimal morbidity
	3. Bulk reduction
Radiotherapy	1. Local tumour control
	2. Minimal morbidity
	3. Sterilization of "sanctuary sites" not inaccessible to chemotherapy
Systemic chemotherapy	1. Eradication of metastatic disease — "cure"
	2. Improved local control

*Small breast cancer, up to two cm in diameter, no axillary gland involvement, no detectable metastases.

beyond the confines of the operation — usually the primary tumour and draining regional nodes. Although it is now clear that many tumours with involved nodes are incurable it is vital that we do not allow the resultant trends to lesser and lesser surgery to compromise the cure of small localised lesions by the use of inadequate local therapy. The recent insight we have gained into tumour biology dictates an approach of balanced pragmatism — surgery alone is the principle curative modality, involved lymph nodes often mean distant metastases incurable by surgery alone, (a right hemicolectomy has never been able to include all draining nodes), but inadequate local surgery, for example for malignant melanoma, can compromise cure.

Surgery devascularises tissues. This has two deleterious effects, oxygen tensions may be lowered, thus compromising the efficacy of subsequent postoperative radiation therapy and delivery of systemic chemotherapy will be less efficient.

Surgery also produces disfigurement. This is particularly so with amputations, operations around the head and neck and mastectomy, although fortunately, the needless deformity of a Halsted radical mastectomy is no longer routine.

Thus, local therapy by surgery alone should be improved if the addition of radiotherapy either, (a) reduced the risk of local recurrence and hence morbidity, or (b) facilitated equivalent local control with reduced surgery and consequent reduced morbidity. An example of the latter is seen with breast cancer, where with six years of follow up, small (less than two cm) breast tumours treated by quadrant excision (and breast preservation) and postoperative radiotherapy do not have any increased local recurrence or decreased survival.[6]

Radiotherapy

Irradiation dose response curves are sigmoid shaped. The initial shoulder represents the accumulation of sublethal molecular changes when larger initial doses (and consequent increased potential normal cell damage) are required for a given fractional cell kill. Cells are more sensitive at specific stages of the cell cycle for example during the G2 (gap) phase rather than during the S (synthesis) phase. Cells than can repair sublethal damage to DNA will not be killed, and can repopulate a tumour. Hypoxia compromises the effects of irradiation although heavy particles (neutrons) partially overcome this.

Thus radiotherapy used alone may fail for many reasons. If the field used does not encompass the extent of the tumour, or the cell population is too large such that unacceptable massive tissue damage results from the dose required to sterilise the tumour, then failure results.

Cells may be hypoxic, particularly in the interior of a large tumour mass without good central circulation; cells may be resistant to irradiation damage, or be in a non sensitive part of the cell cycle; and finally, radiotherapy can only treat local disease, and will never cure patients with distant spread.

Apart from failure, radiotherapy like surgery has other disadvantages when used alone. It may produce immune depression, with prolonged depression of lymphocyte subpopulations[7] and it causes damage to normal tissues — particularly the gastrointestinal tract, bone marrow and areas such as the mandible.

For each of these reasons a combined approach for local therapy, of surgery plus radiotherapy often must be considered.

The Combination of Surgery and Radiotherapy

The principle aims of combining these modalities are to improve local control and to reduce local morbidity without adversely affecting the local control. This is particularly relevant if surgery alone is disfiguring or is followed by an unacceptable regional recurrence rate.

Preoperative radiotherapy has the advantage of treating better oxygenated cells. The often stated theoretical advantage of reducing the size of tumour and operative field thus making the tumour resectable or more readily cured has not been critically evaluated. The disadvantage of radiotherapy is the real problem of inteference with wound healing.

The advantages of postoperative radiotherapy are that tumour extent may be better defined and wound healing is complete, and hence higher doses (up to 6000 rads) may be used. The potential disadvantages are the delay involved (of unknown relevance) and the likelihood of reduced oxygen tensions in the tumour. The use of hypoxic cell sensitisers requires evaluation to see if this problem can be overcome.

Thus the timing and dose of radiotherapy and its sequencing with surgery relate to, (a) resectability — preoperative radiation is used if resection is questionable, (b) the dose desired — very high doses must follow and not precede surgery, (c) the extent of planned surgery, particularly in the head and neck where extensive procedures such as radical neck dissection or pharyngectomy can end in disaster if preceded by radiotherapy. If healing requirements will allow up to 5000 rads preoperatively this is probably preferable, but low dose preoperative radiotherapy is inferior to high dose postoperative irradiation.

A combined radiotherapy surgery approach offers optimal local and regional control for tumours of the urinary bladder, kidney, rectum, testis (seminoma) endometrium, cervix, and some tumours of the breast, and head and neck.

Emphasis must be on cosmetic considerations and quality of life when surgery and radiotherapy are combined — improved cure rates occur, but are more likely to result from the use of effective systemic therapy when this is available.

Systemic Chemotherapy

The common side effects of cytotoxic chemotherapy (marrow depression, gastrointestinal upsets, alopecia) are pushed into relative insignificance if the therapy is effective and can cure otherwise fatal malignancy, particularly if the population involved is young. In disseminated testicular carcinoma 66% of patients will achieve a complete remission with combinations involving cis-platinum, vinblastine and bleomycin, 75-80% will be rendered disease free with surgical resection of residual disease, less than 10% will relapse in one year, and those still disease free at one year have a 99% chance of remaining so for at least three years, (as long as current trials have been run), and by all criteria are cured. Chemotherapy with first or second line combinations can render some 96% of patients with disseminated tumour disease free.[8, 9]

Such a dramatic effect on a previously incurable disease by short course cytotoxic therapy justifies the tolerance of considerable side effects for a "window period", of therapy in the patient's life. This is not the case for all tumours, although there is a reason for optimism that additional effective agents will become available for other tumours.

Interaction of Chemotherapy with other Modalities

The cure potential of adjuvant therapy — the setting for optimal multimodality therapy — is dependent on the efficacy of the chemotherapy used. Surgery is being used in an optimal manner for tumour control (but not necessarily for minimal morbidity), for many tumours. Radiotherapy has potential for greater effectiveness with the use of radiosensitisers (metronidazole, platinum), hyperthermia, cell synchronisation techniques, radioprotectors for normal tissue, intraoperative therapy (large bowel) and neutron therapy. But chemotherapy offers further "magic bullets" like cis-plantinum for testis tumours. However, at present, in the absence of many dramatically effective agents the problems that may occur when chemotherapy is combined with other modalities are of practical importance.

1. Chemotherapy and Surgery

Problems with wound healing have been overstated. They are particularly relevant at present because of current evaluations of intensive perioperative adjuvant chemotherapy for breast cancer. Experimentally, corticosteroids, methotrexate, Adriamycin and cyclophosphamide have been shown to impair wound healing, particularly if given within three to four days of wounding.[10] There is less evidence that this is relevant clinically. Nitrogen mustard, thiotepa and cyclophosphamide have been given perioperatively without producing complications.

There is no data available yet on the effect of combination cytotoxic chemotherapy on wounds, and further investigation is reqired. This is particularly so, when the various settings are considered for patients having cytotoxic agents requiring surgery (for example planned perioperative adjuvant therapy, elective second look laparotomy for ovarian malignancy, elective splenectomy, or surgery for unrelated conditions, unexpected emergencies such as bowel obstruction, and planned excision of metastatic disease.

2. Chemotherapy and Radiotherapy

There is little reliable data on the effect of cytotoxic agents on the mechanisms of radiation damage. Both may act at a molecular level and alkylating agents, and vinca alkaloids (vincristine, vinblastine, vindesine) may be synergestic with radiotherapy. Decreased cell killing or negative interactions can also occur. Decreased immune responsiveness and marrow suppression can both reduce therapy tolerance. Optimal sequencing often must be sought in an empirical fashion, as few randomised trials have addressed this question for even fewer tumours. Perhaps the optimal approach will involve cytotoxic agents before, during and after radiotherapy (or radiotherapy plus surgery) — an approach that will require very careful evaluation for validation.

Toxic interactions have been well documented. Pulmonary toxicity from bleomycin and radiation can be fatal, dactinomycin accelerates radiation induced skin reactions; doxorubicin and radiation combine to produce myocardial damage. Normal cell systems with high turnover for example marrow stem cells, and gastrointestinal mucosa are particularly sensitive to synergistic damage.

Both modalities can produce second malignancies. Relative risks of patients with Hodgkin's disease developing leukaemia are 140 following intensive chemotherapy, and 270 following both intensive radiotherapy and intensive

chemotherapy.[11] Patients having either, and more particularly both, modalities of therapy must be followed up for life — for recurrent disease and second malignancy. This is particularly true for younger patients and patients receiving adjuvant therapy. At present, the risk of second malignancy remains small compared with the risk of death without therapy.

For a combined modality approach to be used optimally, considerable care is necessary to keep all of these problems to a minimum. The oncologist must constantly balance risk and benefit, cure potential with morbidity, and one modality against others. Most of the recent advances that have resulted in falling death rates for all of the common tumours except lung cancer, have resulted from combined modality approaches. This alone justifies further endeavour for more optimal therapies.

FUTURE DEVELOPMENTS

We already are seeing "integrated management" rather than just combined modality therapy. The use of in vitro assays to not only screen new agents for clinical trials but also to select existing agents for individual therapy is being developed. Commercial kits for this are being sold in the United States already, despite the fact that development has barely commenced. Greater attention must be given to screening techniques — not just for high risk groups but also for "cured patients" to detect evidence of recurrence. The curability of choriocarcinoma has long been dependent on efficient use of tumour markers and more recently the use of markers for testicular teratoma has improved patient monitoring. The development of markers for other tumours will dictate clear follow up and intervention policies. The epidemiology and genetics of tumours is becoming better understood resulting in new approaches to families of cancer patients. New radiological techniques are changing diagnostic and monitoring approaches. With such rapid and relevant advances in laboratory science and investigational methods it is becoming increasingly difficult for oncologists to remain skilled in the management of many tumours.

Little advance has occured in recent years in the use of immunotherapy. This is now likely to change as more precise methods of treatment with monoclonal antibodies and individual tumour specific methods are applied. Greater attention will be given to prevention of metastatic disease rather than just its eradication. New concepts such as the genetic transfer (cell free) of metastatic malignant potential can be exploited.

With these new developments the relationship between doctor and patient will be of greater importance. The potential for patient confusion will increase, and with it the need for all specialists to retain their close patient relationships. The great majority of patients are likely to continue to see a surgeon as their primary specialist, and this emphasises the requirement for surgeons to maintain an awareness of all relevant developments in all modalities of cancer therapy. Failure to do this will detract from the privileged oncology role that surgeons currently maintain and enjoy.

REFERENCES

1. FARBER S. Some observations of the effect of folic acid antagonists on acute leukaemia and other forms of incurable cancer. Blood. 1949; 4:160-67.
2. ANDERSON JM. Recurrent cancer after restorative resection of the rectum. Br Med J 1982; 284:531-32.
3. EVERSON RB, FRAUMENI JF JR. Declining mortality and improving survival from Wilms' tumour. Med Paediatric Oncol 1975; 1:3-10.
4. GOLDIE JH, COLDMAN AJ. A mathematical model for relating the drug sensitivity of tumours to their spontaneous mutation rate. Canc Treat Rep 1979; 63:1727-33.
5. GOLDIE JH, COLDMAN AJ, GUDAUSKAS GA. Rationale for the use of alternating non-cross resistant chemotherapy. Canc Treat Rep 1982; 66:439-49.
6. VERONESI U, SACCOZZI R, DEL VECCHIO M et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med 1981; 305:6-11.
7. HOPPE RT, FUKS ZY, STROBER S, KAPLAN HS. The long term effects of radiation of T and B lymphocytes in the peripheral blood after regional irradiation. Cancer, 1977; 40:2071-78.
8. EINHORN LH, WILLIAMS SD, TRONER M, BIRCH R, GRECO FA. The role of maintenance therapy in disseminated testicular cancer. N Engl J Med 1981; 305:727-31.
9. EINHORN LH, DONOHUE JP. Cis-diammine dichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Int Med 1977; 87:293-98.
10. SHAMBERGER RC, DEVEREAUX DF, BRENNAN MF. The effect of chemotherapeutic agents on wound healing. Int Adv In Surg Oncology 1981; 4:15-58.
11. BOIVIN JEAN-F, HUTCHINSON, GEORGE B. Leukaemia and other cancers after radiotherapy and chemotherapy for Hodgkin's Disease. J NCI 1981; 67:751-60.