NEWER APPROACHES IN INTEGRATED TREATMENTS
FOR LOCALLY ADVANCED CANCERS

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Over the ages medical practitioners have searched for and applied a large number of medicinal agents (including herbs and toxins), physical and chemical agents, dietary changes, spiritual activities and a variety of potions and local applications in attempts to find a cancer cure. However a somewhat crude form of operative surgery was the only effective anti-cancer treatment available until approximately 150 years ago.

The situation changed after the discovery of general anaesthesia in 1842 when painless surgery became possible. An era of severe surgical cross-infections followed the new upsurge of pain free operative surgery. This was changed by the work of such greats as Lister, Pasteur, Semmelweis and Koch who discovered the association between micro-organisms and wound infection. They introduced aseptic techniques for surgical operation. This combination of surgery under anaesthesia with aseptic technique was the basis upon which the modern era of great advances in operative surgery was founded allowing treatment of many diseases including cancer.

The second effective modality in cancer treatment, radiotherapy, was introduced less than 100 years ago. This followed the work of the Curies in discovering X-rays at the turn of the century.

Thus for most of this century localised cancers have been treated either by surgeons or by radiotherapists. Sometimes operative surgery and radiotherapy have been used in combination in integrated treatments particularly for such tumours as small localised breast cancers. After surgical removal of the obvious cancer, follow up radiotherapy is often used in an attempt to cure without total removal of the breast.

The first effective medical anti-cancer agents were discovered about 50 years ago. First certain hormones were found to affect growth of some tumours followed by discovery of the first effective cytotoxic anti-cancer drugs. Thus a third effective anti-cancer treatment modality was developed.

Early in the use of the new anti-cancer agents an accidental discovery led to a technique of more effective use of these agents in treating some cancers. It was observed following accidental injection of one of the agents into an artery rather than a vein there was considerable reaction in the tissue supplied with blood by the artery. This led to a belief that drugs given into an artery supplying a tumour region should have a greater anti-cancer effect in that region than drugs distributed equally throughout the circulation by the usual systemic or intravenous route.

As surgeons treated most patients with cancer and surgeons had the facility of exposing and injecting arteries with drugs, surgeons were amongst the first clinicians to use anti-cancer drugs to treat their most difficult cancer problems. Unfortunately initial experience in doing this was disappointing. When used by medical colleagues the drugs appeared to be active against a number of tumours which were widespread throughout the body but they appeared to have little beneficial action on locally advanced tumours treated by surgeons whether or not intra-arterial infusion of the agents was used. Surgeons therefore lost interest in the use of anti-cancer agents, particularly in treating locally advanced cancers, even when given by intra-arterial delivery. The use of these new agents was left largely to haematologists and other physicians who treated more responsive widespread malignant disease.

Some years later it was appreciated that the predominant reason the early experience of surgeons was so disappointing was that the drugs had been used largely to treat patients who had tumours which had recurred after initial attempts
at surgical resection and/or treatment by radiotherapy had failed. These recurrent tumours were in tissues to which the blood supply had been compromised by previous operative surgery and/or by radiotherapy. Thus the agents used being carried in the locally reduced blood stream could not reach the tumour tissue in effective concentrations. However by this time surgeons in general had lost interest in the use of the drugs and their application was reserved mainly for palliative treatment of widespread cancer and later treatment of a small group of uncommon cancers which were unusually sensitive to certain anti-cancer agents.

Thus for the past 50 years there have been 3 main methods of anti-cancer treatment. In general localised cancers have been treated by surgical removal wherever possible or by radiotherapy. More widespread cancers have been treated by medical oncologists by systemic injection or infusion (ie. given intra-venously equally to all body tissues) either to get palliation of symptoms or as "adjuvant" treatment. Adjuvant treatment is treatment given after the main cancer has been effectively removed by surgery or radiotherapy but there is a significant risk that small numbers of malignant cells may have already spread to other parts of the body. These scattered cancer cells are likely to cause tumour recurrence (metastases) in a distant tissue. "Adjuvant" treatment is usually given by a medical oncologist after a surgeon or radiotherapist has dealt with the original primary cancer. Breast cancers and bone sarcomas are the most common malignant tumours to be treated by adjuvant chemotherapy after operative surgery because with these tumours there is a considerable risk that malignant cells have already broken away from the original (primary) tumour and may be starting to develop new cancer colonies (secondaries or metastases) in other tissues. Breast cancer cells and bone sarcoma cells are sensitive to anti-cancer drugs so that adjuvant chemotherapy can be very effective in destroying small colonies of cancer cells before they develop into significant metastatic cancers.

A fourth treatment modality, immunology, has been the subject of intensive research over the past two decades. There has been great hope that a new and more effective immunological anti-cancer treatment modality would be found. In spite of studies in immunology giving much increased knowledge about tumours, until recently most of the expectations and great hopes that have arisen from time to time have not resulted in any significant improvement in treatment. However, quite recently immunological studies have been more encouraging. There are now prospects of an effective immunological anti-cancer agent becoming available. This new discovery is called tumour necrosis factor (TNF). This product of immunology research appears to be too toxic for effective clinical use on its own and too toxic to give systemically to the whole body tissues. However when used in small doses with other anti-cancer cytotoxic agents better results have been achieved in treating some cancers than from using cytotoxic agents alone.

In spite of the original disappointing results of most surgeons who first used anti-cancer drugs by intra-arterial infusion some surgeons continued to believe that there should be a role for use of anti-cancer agents given intra-arterially to treat aggressive or advanced cancer in a localised region. The benefit of this technique is now being widely appreciated.

It became clear that provided anti-cancer drugs were infused into the tumour blood supply whilst the blood supply was intact and had not been damaged by previous operation or radiation the regional tumour response could be considerable. It was therefore apparent that to achieve the most effective response of locally advanced cancers with chemotherapy the anti-cancer agents should be used before either operative surgery or radiotherapy had damaged the tumour blood supply. Thus intra-arterial chemotherapy is best given before surgery or radiotherapy rather than after. When anti-cancer drugs are given as the first treatment either systemically or preferably into the arteries of supply by intra-arterial infusion or perfusion many large and aggressive tumours can be reduced in size and aggressive qualities. Such tumour reduction can make the tumours more curable by following radiotherapy and/or surgical resection. In early experience when the drugs were used last the results were poor but when the drugs are used first in a combined treatment program, the results of treatment of large and aggressive tumours are significantly better. Such treatment was subsequently referred to as "neo-adjuvant" chemotherapy although a
more appropriate description of the use of chemotherapy first is "induction chemotherapy". By induction chemotherapy is meant using chemotherapy to induce changes to achieve reduction of tumour size and aggressive characteristics and so make the tumours more curable by following radiotherapy and/or surgical resection.

Sadly due to the early failed experience of surgeons in using chemotherapy there has been a reluctance of many surgeons and other clinicians to re-look at the prospective value of using chemotherapy prior to planned subsequent radiotherapy or surgery and especially to use the chemotherapy by intra-arterial infusion or perfusion on a regional basis. In general surgeons lost interest in the use of the drugs and physicians in general do not have facilities for giving drugs on a regional basis. The integrated treatment programs therefore have been left largely in the hands of small numbers of dedicated clinicians combining the expertise of surgeons, medical oncologists, radiotherapists and others. New to this dedicated group are some relatively recent specialists, the interventional radiologists, who have become vital to the success of such a team. Interventional radiologists have expertise in putting cannulas into arteries in many parts of the body without requiring a surgical operation. The other essential professionals in such team work are dedicated nursing staff, experienced in observing the responses and potential problems that may arise in giving strong anti-cancer drugs into a localised region.

Such has been the background of development of integrated anti-cancer treatment for locally advanced and aggressive cancers. Better prospects of cure are achieved by such integration with effective chemotherapy as the first modality of treatment, to reduce the tumour size and aggressive characteristics followed by either radiotherapy or surgical resection, or both as the definitive follow up treatment to eliminate the reduced residual cancer.

The use of regional chemotherapy naturally depends upon the tumour being supplied with blood by one or sometimes more regional arteries which can be effectively cannulated for regional treatment and the likelihood that the cancer is totally contained in that region. Such cancers with regional blood supply and likely to remain localised in the tissue of origin and yet are commonly not successfully treated by surgical operation or radiotherapy are locally advanced cancers in the head and neck region (where there is one major artery of supply), cancers of stomach (again there is one artery of supply), and advanced malignant tumours in limbs (again with one major artery of supply).

Locally advanced breast cancers may also be effectively treated with a similar plan of integrated regional chemotherapy, radiotherapy and surgical resection but with this particular cancer there is also a considerable likelihood of tumour cells being more widespread into other body tissues. For such tumours and also for malignant tumours in bone (called osteosarcoma and common in young people) to achieve local response and local tumour eradication by using follow-up radiotherapy and/or operative surgery is only part of required treatment. These tumours are likely to have small deposits of cancer spread to other body tissues. For this reason additional post-operative adjuvant systemic chemotherapy is also given with considerable effect. In the case of advanced soft tissue sarcomas in limbs and osteosarcomas in limbs studies in Sydney University Surgical Oncology Service have shown that the standard treatment by limb amputation can now be avoided in about 80% of patients with equally good survival results. In the case of stomach cancer our studies have shown approximately twice the number of cures when intra-arterial chemotherapy is given first followed by operation than by operation alone.

There are other techniques for using regional chemotherapy, especially in limbs. By limited isolation of the limb from the general body circulation using tourniquets, very high concentrations of drugs can be delivered into the arteries for a limited period of time. Used in combination with tumour necrosis factor (TNF) such treatments have given even better prospects of cure of sarcomas and other tumours in limbs.

Other workers are exploring the possibility of using similar integrated techniques in treatment of tumours in the pelvis, especially in ovary, uterus, bladder and prostate. However at this stage more experience and information are required before
application of these combined and integrated techniques can be generally recommended or applied. Similar studies are being made with integrated treatment for cancer of the pancreas which is not only becoming more common in our community but remains one of the most difficult cancers to treat. Techniques are being developed to apply the advantages of regional chemotherapy by special techniques even though there are considerable difficulties in cannulating and treating the tumour-bearing area without damaging adjacent bowel and other tissues.

Cancers in tissue supplied by arteries which cannot be appropriately cannulated, but where results of standard radiotherapy and/or operative surgery are unsatisfactory, include lung cancer and cancer of the oesophagus. A number of studies are in progress to try to improve prospects of cure using of systemic chemotherapy preceding radiotherapy and/or operative surgery. Again although there have been some encouraging prospects, as yet there are still unsolved difficulties and results to date have not shown definite improvement.

**SUMMARY:**

In summary it should be stated that local malignant tumours which can be effectively treated by surgical resection or by radiotherapy alone or in combination are best treated by those standard treatment methods. This applies to most early cancers which are therefore best treated by appropriate surgeons and/or by radiotherapists. On the other hand tumours which are so locally advanced that they are unlikely to be cured by operation or radiotherapy, or tumours which are so locally aggressive that standard treatment does not offer good prospects of cure, or tumours for which standard treatment requires severe mutilation such as limb amputation; the possibility of improving results by the use of integrated regional treatment including chemotherapy (where appropriate on a regional basis) with radiotherapy and/or operative surgery should be considered. Such integrated treatment may offer significantly improved prospects of cure and without mutilation.

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