PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

VOLUME 10 No:1 AUGUST 2002

INSIDE THIS ISSUE ...

The Mission of St Vincent's Clinic Foundation

The people of Sydney and beyond are fortunate to benefit from one of the most comprehensive health care services available at the St Vincent's Campus at Darlinghurst. These facilities are part of the 34-strong health and aged care facilities under the direction of the Sisters of Charity of Australia.

Integral to the Darlinghurst campus is the services and facilities provided by St Vincent's Clinic and St Vincent's Clinic Foundation. The aim of St Vincent's Clinic and St Vincent's Clinic Foundation are patient care, medical teaching and clinical research. The three aims are interlinked and each serves to strengthen the others.

Established in 1992, St Vincent's Clinic Foundation provides funds and support for medical research into matters of clinical significance as well as providing support for public and medical education.

Every advance in medical science has started with a commitment by a medical practitioner or a scientist to alleviating the pain and suffering of mankind.

Australia is rich in research bodies which focus on clinical laboratory based research. However, funding is sparse for research conducted in the course of patient care. This is where St Vincent's Clinic Foundation can focus some of the community's goodwill.

Since 1992, the Foundation has spent over $2.5 million and provided financial support for over 100 research projects. The Foundation has successfully supported vital research into disease and illness including cancer, diabetes, kidney disease, heart disease, arthritis, mental health, youth suicide, deep vein thrombosis and obesity, to name just a few. Additionally the Foundation supports research into the function of genes and cells in many diseases. The Foundation also provides financial support for medical students who wish to undertake research during their study.

The Foundation depends on donations to continue to support this important research.

We need your support to assist St Vincent's Clinic Foundation to continue to provide financial support to our researchers.

ST VINCENT'S CLINIC, SYDNEY VOLUME 10 No:1 AUGUST 2002

PROCEEDINGS

ADDRESS

ST VINCENT'S CLINIC
438 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia
Phone: (02) 8382 6222 Fax: (02) 8382 6402

EDITORIAL

Dr John O'Neill MD, FRACP

Consultant Neurologist

Editor, Proceedings

This Issue is the second of a 2-part series (See "Proceedings", August 2001) on certain aspects of cancer care on St Vincent's Campus.

The first article by Dr Paul Crea critically analyses "Sentinel Node Biopsy", a new technique crucial to decision-making in breast cancer management. Recent literature had suggested that if, at initial surgery, there was no evidence of cancer involving the sentinel node of the axilla then survival following mastectomy alone was no worse than if this procedure was combined with surgical axillary clearance (radical mastectomy). Avoidance of the latter procedure would obviously improve cosmetic outcome and greatly reduce morbidity for the patient. Dr Crea reviews this literature and describes his own careful development of the technique at St Vincent's Clinic. He reports his personal management of 200 consecutive cases of breast cancer, using the technique of sentinel node biopsy, over a period from mid-1999. This is a scholarly work and epitomises excellence in a combined clinical and research project which has enormous practical importance for women who develop breast cancer.

Dr Michael Jensen reviews the literature on soft tissue neoplasms and, in particular, malignant sarcomas. He reviews his personal data in management of 83 consecutive cases over a 15-year period. This experience equates to 20 – 25% of all cases seen in NSW over a similar period of time. Dr Jensen's experience in this field is clearly remarkable and his own personal results appear to be equally as good as have been reported in the international literature.

Drs Gordon O'Neill and Raji Kooner of the Urology Department of St Vincent's Clinic have produced excellent reviews on the diagnosis and management of bladder cancer (Dr O'Neill) and renal cell carcinoma (Dr Kooner).

Dr Ian Cole, ENT Surgeon, has reviewed the literature on management of laryngeal cancer, incorporating his own personal experience (Table 2). The article emphasises current surgical techniques aimed at maximising survival but also conserving laryngeal function and hence quality of life for patients who suffer with this condition.

This year, the 8th Sandra David Memorial Lecutre was given by the Governor of NSW, Her Excellency Professor Marie Bashir. She discusses the challenge society faces in the area of mental health (especially depression) in young people. Having been both a clinician (Psychiatrist) and administrator in mental health, especially involving children and young people, her insights and reflections on this problem make excellent reading and food for thought.

Established in 1992, the St Vincent's Clinic Foundation provides funds and support for medical research as well as for public and medical education. Since inception, the Foundation has spent over $2.5 million for these purposes, supporting over 100-research projects. Much of the hard fundraising for this achievement has been, and continues to be, undertaken by the St Vincent's Private Hospital Ladies Committee. At the end of this Issue is a list of the recipients of the 2002 Research Grants. These projects are currently under study.

Privacy Statement

St Vincent's Clinic distributes Proceedings to keep you up to date about research activities at St Vincent's Clinic. St Vincent's Clinic collects personal information from its donors and other interested supporters to provide you with information about our activities.

We value your privacy and treat any information we hold as confidential. We don't share your information with any third parties, unless we are required to by law or on a confidential basis to agents that we use in the ordinary operation of our business (such as for data processing, printing or mailing). We have developed a privacy policy which has more information about how we deal with privacy issues.

You have a right to obtain access to the information we hold about you. If you would like to access that information, or if you would like a copy of our privacy policy or more information abut St Vincent's Clinic, please contact us on 8382 6405.

Dr Paul Crea

Breast Cancer Management

The new techniques of sentinel node biopsy – evolution or revolution

Introduction

The latest figures from the NSW Cancer Registry show that in 1999 there were 3,493 new cases of breast cancer diagnosed, of which 25 were male. Breast cancer accounted for 27% of female cancers and led to 820 deaths (16% of female cancer deaths). Over the past 30 years, there has been a gradual increase in incidence from 51 to 77 per 100,000. The death rate however, has fallen from 18.5 to 16.1 per 100,000, probably representing the onset of population screening and improved treatment. However, there remains an overall risk for a female developing breast cancer of 8.9% (1 in 12) by the age of 75. Currently, there are about 35,000 women in Australia living with breast cancer, their average 5 year survival being 79%.

There is a high level of social awareness in Australia of both these figures and the consequences of surgery, radiotherapy and chemotherapy. This has led to strong calls for efforts to be made to significantly improve both.

Dr Paul Crea, FRCS, FRACS
Surgical Oncologist
St Vincent's Clinic

The Breast – Mastectomy

On a September morning in 1811, Fanny Burney, an English essayist living in Paris, underwent a mastectomy in Paris without the benefits of anaesthesia. A vivid account of her terrifying ordeal is preserved in letters she wrote to her sister in London. She survived the operation and the disease for many years.

It was not until the 1880s that William Halsted, of Johns Hopkins Hospital in Baltimore, published a landmark report detailing the operation of radical mastectomy. This achieved the first significant success in the control of breast cancer. The surgery was extensive and disfiguring but its benefit was soon evident and it became the operative procedure of choice and the standard treatment of breast cancer for the next 70 years. It was seen as vastly preferable to the alternative of a slow death from the consequences of advanced cancer.

In the early 1950s, various institutions began to question the need for such extensive surgery and investigated the possibility of decreasing its extent without compromising the results in terms of survival. Some modifications to the standard radical mastectomy succeeded such as the preservation of the pectoralis major muscle (modified radical or Patey's mastectomy). Others failed, such as attempts to conserve the breast without adding the safety of radiotherapy, which led to an increased rate of local recurrence.

Today the most commonly used breast conservation procedure is the so-called "lumpectomy". This is somewhat of a misnomer as it can lead to an automatic presumption that the treatment of the primary cancer in the breast requires no more than the removal of the lump itself. The procedure would better be termed a "partial" or "segmental mastectomy". With the onset of breast screening and increasing community awareness, the diagnosis of breast cancer is now being made at a much earlier stage. This renders conservative surgery a suitable option in more than 80% of cases resulting in an equal survival rate to the previous more radical procedure and it has become accepted as the standard alternative.

The Axillary Glands – Background to Sentinel Node Biopsy

Once the primary cancer within the breast is treated by either partial or total mastectomy, the second arm in the management of breast cancer has always been the removal of the axillary glands. This was done for the dual purpose of determining whether spread had occurred to them and, potentially, as management if involved glands were found.

Evaluation of data from large series has shown that the overall incidence of axillary metastases is 46%.[1] This, however, drops sharply with the decreasing size of the primary tumour as well as its characteristics, such as grading and the absence of visible vascular invasion.

Two important factors, however, need to be considered. The first being that even though the incidence of axillary metastases can be up to 40%, the incidence of clinical uncontrolled axillary disease if axillary dissection is not performed is 21%[2], indicating that half of the axillary lymph nodes may never present as clinical disease. The second factor is that axillary nodal involvement can still occur, though uncommonly, even in patients with early primary tumours.

Recurrence in the axilla after axillary clearance is between 1 & 3%.[3] So, although axillary clearance is a very effective way of controlling this potential for axillary disease, it commits a large number of women, whose axillary glands will prove to be free of metastatic disease, to unnecessary surgery.

The false negative rate of histological evaluation of the axillary glands is generally considered to be low, at less than 2%. However, this is most likely an underestimation, in the absence of immunohistochemical testing. Also, the long held practice that the status of the axillary nodes would dictate the direction of further adjuvant treatment is now not as valid, with the nature of the primary tumour now being considered an equally important factor in this decision. Some further inaccuracy in staging also occurs due to the lack of evaluation of the status of the internal mammary nodes which can harbour metastatic disease in 10-20% of patients. (It is, however, accepted that routine dissection of the internal mammary chain will not improve survival.)

The morbidity of axillary dissection is well known and has been recently summarised in a publication from the National Breast Cancer Centre. It includes:

1) Seroma – this is common, uncomfortable and generally not influenced by the type and duration of drainage.

2) Wound infection – an incidence of about 10% is reported though this may not be significantly altered if lesser procedures are undertaken.

3) Reduced shoulder mobility and stiffness – this will occur to some degree in virtually all patients and its severity will depend on age and pre-existing conditions, such as arthritis, as well as post-operative motivation and mobilisation.

4) Paraesthesiae – this is virtually universal and is associated with division of the intercosto-brachial nerve, although its preservation will not eliminate it. A small number of patients will experience debilitating neuropathic pain resistant to standard forms of analgesia.

5) Motor nerve damage – this can occur in four areas:

   (i) medial pectoral nerve: injury to this is common during dissection around the pectoralis minor muscle and leads to wasting of its lower fibres though producing minimal morbidity.

   (ii) nerve to serratus anterior: damage to this will result in winging of the scapula.

   (iii) nerve to latissimus dorsi: damage usually results in minimal morbidity with some associated loss of power.

   (iv) brachial plexus palsy can occur in fewer than 1% of cases but its presentation is very dramatic in the loss of all shoulder abduction post operatively. Its cause is unknown, occurring even with the most careful arm management during surgery. Virtually all cases will recover however, within three months.

6) Lymphoedema – this is the most significant and well known side effect of axillary dissection. It is clinically obvious in about 10-20% of cases and probably occurs, if measured, in 30-40%. It is well recognised in the community and held in fear by all women, leading some to totally reject axillary surgery.

All non-invasive attempts to assess the status of the axillary glands, including clinical examination, mammography, ultrasound, CT, MRI and PET scanning have not succeeded.

Clearly, a need existed to explore the possibility of limiting axillary surgery whilst maintaining safety. One of the first such reports was in the early 1980s when Forrest in Edinburgh described a technique of axillary (pectoral node) sampling. None of the 67 patients with negative sampling converted to positive on subsequent axillary dissection.[5]

Sentinel Node Biopsy – Development

The "sentinel node" concept was first described over twenty years ago in the treatment of penile cancer and, subsequently, in melanoma by Donald Morton[6] who used an injection of blue dye to identify the gland. Methylene Blue and fluorescent dyes were tried and were unsuccessful. The two most commonly used dyes today are Isosulphan Blue and Patent Blue-V. In the management of breast cancer, the technique of sentinel node biopsy was first reported by Krag in 1993[7] using radionuclide scanning and by Giuliano[8] in 1994, using blue dye and, subsequently, by Albertini[9] using a combination of both.

In 1997, Veronesi[10] from the European Institute of Oncology in Milan reported the largest study using lympho-scintigraphy and intraoperative use of the gamma probe. Many multinational studies since then have validated the concept that the spread of cancer cells to the axillary basin is not a random event but occurs sequentially, beginning with

the sentinel node (or nodes) and then to higher levels.

In 1999, Cody [11], of Memorial Sloan Kettering Cancer Center, reported the experience of 1500 cases of sentinel node biopsy from a single institution. This recognised the existence of a steep learning curve and recommended that an audit of each surgeon's performance be done to achieve a false negative rate of about 5%. Worldwide consensus currently suggests that each surgeon newly undertaking this procedure should do the first 30-40 cases by both sentinel node biopsy and subsequent full axillary dissection to evaluate his level of skill.

Sentinel Node Biopsy – Personal Experience

The remainder of this paper will analyse the results of a personal series of the first 200 cases of sentinel node biopsy accrued since the introduction of this technique at St Vincent's Clinic in mid 1999, following a visit to the European Institute of Oncology.

The initial requirement was the introduction of a totally new procedure within the Campus setting. This involved the collaboration of various departments and the study parameters were that it would be carried out by a single breast surgeon within a private surgical practice. To minimise variances only two Nuclear Medicine departments were used (St Vincent's Campus {public and private hospitals} and the Mater Hospital) and two pathology practices (Douglass Hanly Moir and Sydpath).

Evaluation of the procedure would be judged by the accuracy of three parameters:

1. accuracy of pre-operative radionuclide scanning (the choice and use of isotope);
2. accuracy of intraoperative localisation (the choice and use of the gamma probe);
3. accuracy of pathological testing (intraoperative frozen section).

Evaluation of three end points would then be made:

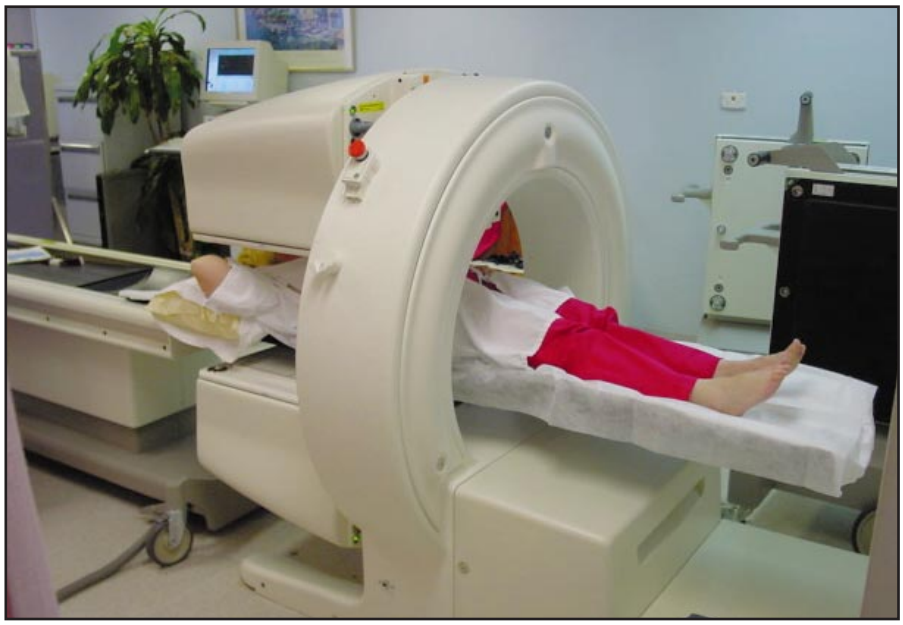


Figure 1: Lymphoscintigraphy scanning following injection of radionuclide colloid.

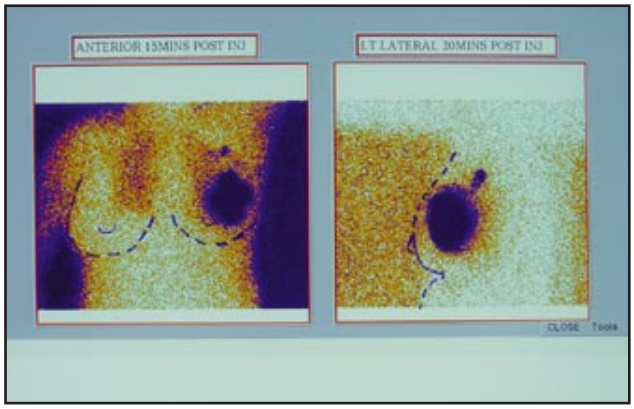


Figure 2: Lymphoscintogram showing injection site (large hotspot) and Sentinel Node (small hotspot)

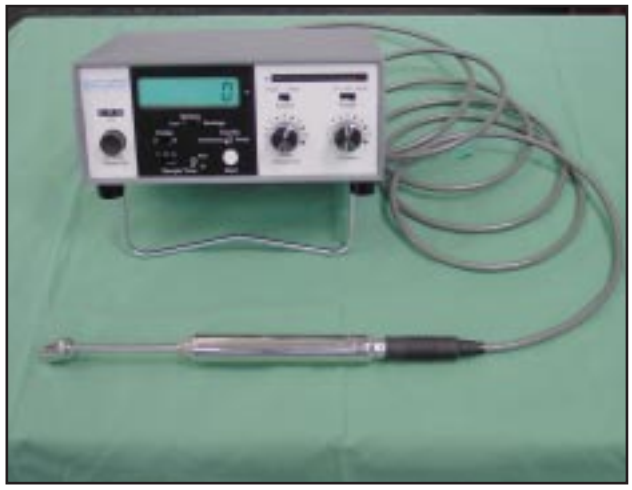


Figure 3: "Navigator" Intra-operative probe used to identify Sentinel Node site in lower axillary area.

1. the reliability of the assessment of the sentinel node, as judged on frozen section and subsequent histological analysis, in predicting the status of the remainder of the axillary glands;
2. the incidence of local axillary bed recurrence;
3. long term prognosis (survival).

Materials And Methods

Radionuclide Scanning: From various literature reviews a decision was made that the best radiopharmaceutical was 99m Technetium Antimony Sulphide Colloid having a particle size of 50-200nm, a half life of 6 hours and an imaging energy of 140-150KeV. Its characteristics were optimal for absorption into the lymphatic channels and trapping within the interstitial space within the lymph nodes. It would be

delivered by subdermal peri-areolar or peri-tumoural injections in 4 divided doses of 0.05 – 0.1mls to a total dose of between 10 – 50MBq. The area of injection would be massaged and scanning undertaken over the following 90 minutes. The images acquired would then be taken with the patients to surgery (Fig 1 & 2).

Intraoperative Localisation: There were 4 different handheld probes evaluated and the USSC Navigator was selected and has been subsequently used in all cases (Fig 3). It has a peak sensitivity of 140KeV (window of 120-150) and the response is transduced into an acoustic signal and digital read out.

(Blue dye was concurrently used in 6 cases, with injection after induction of anaesthesia {Patent Blue V 2.5%} peri-tumourly, 2mls diluted to 5mls with normal saline.)

Using the gamma probe and with the visual aid of the scan, the sentinel node site was then identified intraoperatively (Fig 4) allowing either a small incision to be made into the lower axillary skin or at the lateral end of the incision for tumours in the upper outer quadrant (Fig 5). The active node (or nodes) was removed and tested away from the patient (Fig 6) and then sent for frozen section. Lack of residual activity in the biopsy cavity was then checked.

Pathological Evaluation: There were slight variations in the techniques of frozen section analysis. This was either done by bisecting the node or taking 2mm slices and examining the largest. After H & E staining, the whole face of the node was examined to allow visualisation of the subcapsular area for possible micrometastases. All residual tissue was then fixed in formalin and processed in routine paraffin blocks, staining with H & E and, if negative, proceeding to Keratin Immuno-peroxidase staining (Cam 5.2, cytokeratin 19, or AE1/AE3).

The procedure of sentinel node biopsy was discussed at length with operable patients. It was offered to all patients with tumours less than 4cm in size and in the absence of multifocal disease or palpable axillary nodes. (Initially, it was considered unsuitable in cases of previous breast surgery or insitu ductal carcinoma; this view changed during the course of the study.)

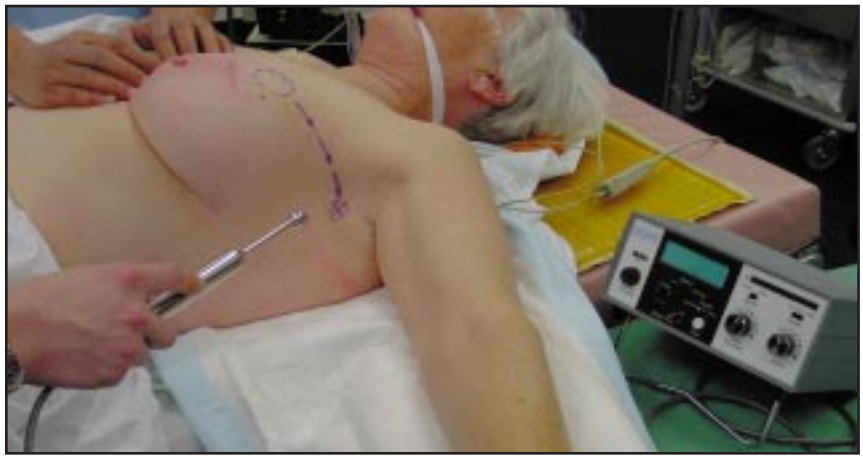


Figure 4: Intra-operative localisation of Sentinel Node.

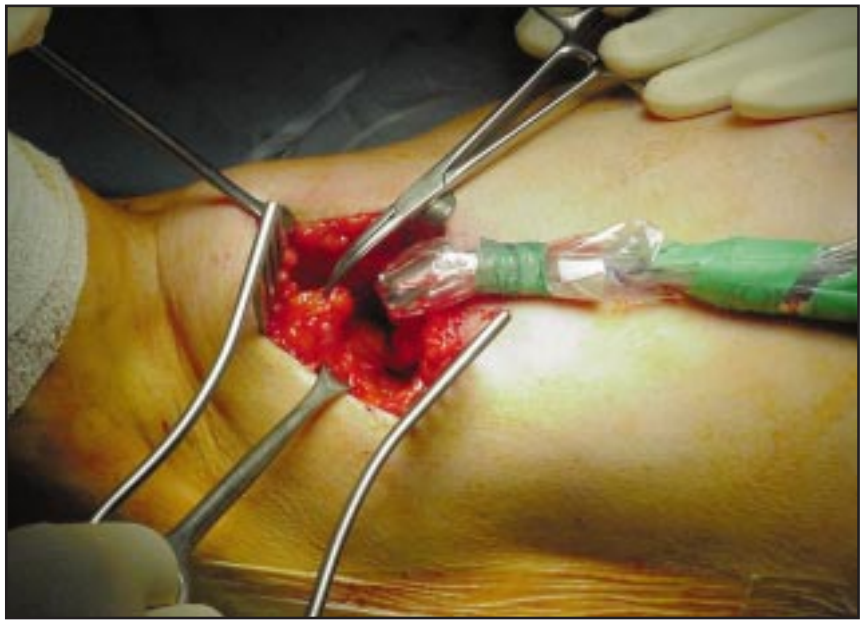


Figure 5: Resection of identified Sentinel Node.

After a full explanation of the procedure and an opportunity to read some literature, a full and informed consent was obtained from each patient to either proceed to complete axillary dissection if the sentinel node was found to be positive on frozen section, no axillary dissection if negative, or variations of these if the testing failed to show a node, reflecting the patient's wishes. Two hundred cases were entered into the study. In the first thirty of these, total axillary dissection was planned irrespective of the status of the sentinel node unless otherwise requested by the patient.

RESULTS

The first 30:

A total of 52 cases of primary breast cancer were seen in the 4 months to the end of November 1999. Of these, 22 were excluded for various reasons and 30 proceeded to sentinel node biopsy. Treatment of the breast tissue was by total mastectomy in 15 and partial mastectomy in the other 15. From these, 24 patients proceeded to standard axillary dissection. Of the remaining 6, 4 requested sentinel node biopsy only and 2, Level I-II dissection.

Sentinel node was identified by scanning in 21 of 30 patients (70%). A further 6 were found by intraoperative gamma probe for a total localisation rate of 90% (27/30). In these 27 patients, the node was found to be positive in 8, and all were confirmed on subsequent H & E. In the other 19, in whom the node was reported as normal on frozen section, 3 converted to positive on H & E. All were in subcapsular foci only.

Successful sentinel node localisation was undertaken in 21 patients. Of the 8

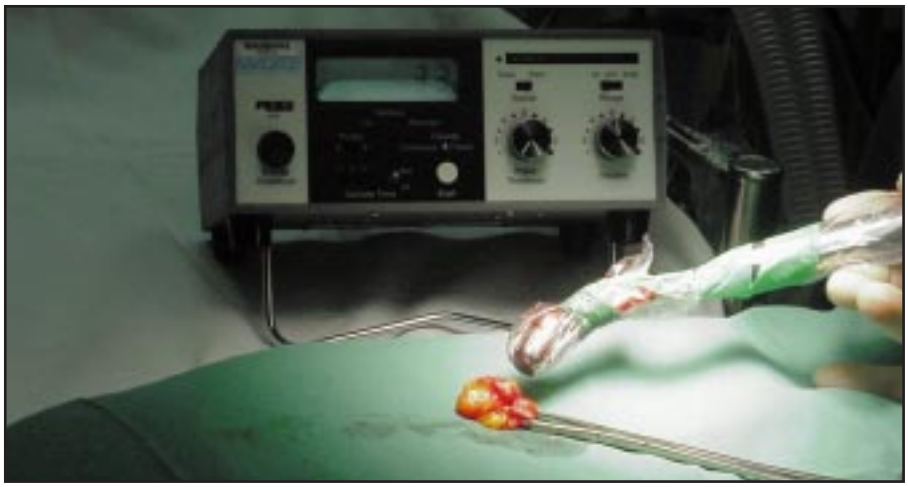


Figure 6: Resected specimen (Sentinel Node) Activity confirmed away from operative field.

TABLE 1: INSTITUTIONS AND PATHOLOGY SERVICES USED

NUCLEAR MEDICINE SCANS PERFORMED AT:		%
St Vincent's Clinic	111	55.5
St Vincent's General	74	37
Mater Hospital	15	7.5
PATHOLOGY SERVICES		%
Douglass Hanly Moir	104	52
Sydpath	96	48

TABLE 2: DYE INJECTION SITE

TRACER INJECTION SITE		%
Peritumoral	142	71
Subareolar/between Nipple and Tumour	49	24.5
Around Hookwire	4	2
Unknown	4	2
Blue Dye	1	0.5

in whom the node was positive, this was the only node positive in 6 (a total of 130 other nodes removed were normal). In the other 2, only three of a total of 22 nodes removed were positive.

In the 13 patients with negative nodes on frozen section, 11 remained negative on H & E. In the other 2, the first had 7 cancer cells found in a subcapsular focus, the other 32 nodes being negative and, in the second, one of eight other axillary nodes was found to be positive, representing a skip metastasis.

These preliminary results showed a false negative rate on frozen section of 15% (2/13) and a positive predictive value of the status of the axilla of 95% (20/21). These figures compared favourably with world results and encouraged proceeding with the technique.

The first two hundred:

The accrual of 200 cases took just over 2 years. During this period of time there were continual refinements made to the technique, though the basic structure and methodology remained unchanged. This report will detail a preliminary analysis of these cases.

Rigorous efforts were undertaken with each patient to provide them with a balanced explanation of its pro's and con's. As time passed, individual patients became much better informed of the nature of the procedure through the media as well as by self-initiated literature and internet searching. Often second visits were requested as each patient took time to examine the information supplied in an effort to arrive at the best decision. Of those suitable for selection, the vast majority opted to undertake sentinel node biopsy. Table 1 shows the institutions where the procedures were undertaken and the pathology services used.

The performance of pre-operative radionuclide visualisation became much more streamlined as department members refined the finer details of the mode of injection, scanning and massaging (especially difficult with hookwire localisation). Peri-areolar injections became more common, especially in tumours of the upper outer quadrants, to allow distancing of the primary hotspot from the sentinel node (Table 2). Surgical techniques were also refined as it soon became apparent that the sentinel node may not be within the visualised Level I area of the axilla or be the most obvious lower axillary node. Pre-operative scanning was successful in identifying a sentinel node in 167 cases (83.5%). With subsequent use of the intra-operative probe, the sentinel node was identified in a further 20 cases thus increasing the total success rate of pickup to 93.5% (Table 3). The type of operative procedures undertaken on the breast and the axillary glands were now virtually independent of each other, as is shown in Table 4. Breast conserving surgery was undertaken in 69.5% (139/200). Sentinel node biopsy, with no further axillary dissection was performed in 61.5% (121/200). Twenty-one patients requested some modified form of lower axillary dissection, even if the sentinel node was negative.

Results were analysed on an ongoing basis and the first factor to be considered was the rate of false negative frozen sections. This group was identified on subsequent paraffin and immuno-peroxidase stains (Table 5). In the 187 cases in whom the sentinel node was successfully identified, 154 were frozen section negative (82.4%) and one was equivocal. Of these however, 17 subsequently proved to be paraffin positive (11%). On histopathology, 5 of this group had definite metastatic deposits, usually being found in a nodal pole away from the cut surface, the other 12 showed only small subcapsular foci. Of the 136 patients shown to be frozen section and paraffin section negative, 88 were tested for keratin staining (immuno-peroxidase) and positivity was found in 5, again all were subcapsular deposits only. In only one case was the gland found to contain widespread replacement and this was with lobular carcinoma, whose cells are notoriously difficult to identify on frozen section.

DISCUSSION

The technique of sentinel node biopsy has major physical and psychological advantages and attempts to address the commonly held community dread of lymphoedema. It also significantly decreases morbidity and length of hospital stay. Various North American centres are now undertaking it as a day only procedure under local anaesthesia.

Several questions remain incompletely resolved. The first is the long term safety of the procedure as judged by the rate of local recurrence in the axillary bed. In the first 100 cases, no local axillary recurrence was found at their one year follow-up visit. The second question would be the long-term assessment of end-point survival in this group of patients compared to the time honoured standard of modified radical mastectomy. We also have to decide what level of false-negative rate is acceptable. A major unanswered question is what form of treatment should be recommended in the cases where only subcapsular metastatic foci are found. Their relevance in dictating adjuvant treatment is unknown as they may have always been present in the past but were not identified due to the lack of immunoperoxidase staining – currently this group is recommended for adjuvant chemotherapy.

Several international studies are currently being undertaken to try and resolve these matters but their results will not be available for several more years. As happened with laparoscopic cholecystectomy, the force of patient demands may see the universal acceptance of this procedure well before that. If so, great care must be taken to avoid the pitfalls and the use of this procedure should be limited to those who are adequately experienced to undertake it.

TABLE 3: SUCCESS RATE – SENTINEL NODE IDENTIFICATION

NUCLEAR MEDICINE SCAN FOR SENTINEL NODE		%
Nodes Detected	167	83.5
No Nodes Detected	32	16
N/A (Blue Dye only)	1	0.5
INTRA-OPERATIVE PROBE		%
Sentinel Node Found	187	93.5
Sentinel Node Not Found	13	6.5

TABLE 4: OPERATIVE PROCEDURES

BREAST OPERATION		%
Partial Mastectomy	139	69.5
Total Mastectomy	58	29
Subcutaneous Mastectomy	3	1.5
AXILLARY SURGERY		%
Sentinel Node Biopsy Only	121	60.5
Level I-II Dissection	15	7.5
Lower Axillary Sampling	6	3
Total Axillary Dissection	58	29

TABLE 5: SENTINEL NODE ANALYSIS – PRESENCE/ABSENCE OF METASTATIC DEPOSITS IN SENTINEL NODE. ACCURACY OF RESULTS ON SUBSEQUENT LEVELS OF TESTING

FROZEN SECTION	187	%
Negative	154	82.4
Positive	32	17
Equivocal	1	0.6
PARAFFIN SECTION (Frozen Section Neg)	**154**	%
Negative	136	88.3
Positive	17	11.0
Equivocal	1	0.7
IMMUNOPEROXIDASE (Paraffin Neg)	**136**	%
Negative	83	61
Positive	5	3.7
Not Tested	48	35.3

BIBLIOGRAPHY

1. Carter C L, Allen C, Henson D E. Relation of tumour size, lymph node status, and Survival in 24,740 breast cancer cases. Cancer 1989; 63:181-7
2. Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M. The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histological nodal status in carcinoma of the breast. Surg Gynecol Obstet 1981; 152: 765-72
3. De Boer R, Hillen H F P , Roumen R M I I, Rullen I I JT , Van der Sangen M J C, Voogd A C. Detection, treatment and outcome of axillary recurrence after axillary clearance for invasive breast cancer. Br J Surg 2001;88:118-122
4. Veronesi U, Cascinelli N, Buffalino R, Morabitu A, Greco M, Galuzzo D et al. Risk of internal mammary node metastases and its relevance on prognosis in breast cancer patients. Ann Surg 1983; 198:681-684
5. Forrest A P M, Stewart H I, Roberts M M, Steele R I C. Simple mastectomy and axillary node sampling (pectoral node biopsy) in the management of primary breast cancer. Ann Surg 1982; 196: 371-7
6. Morton D L, Wen D-R, Wong J H, Economou J S, Cagle L A, Storm F K, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992; 127: 392-9
7. Krag D N, Weaver D L, Alex J C, et al. Surgical resection and radiolocalisation of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 1993; 2. 335-40
8. Giuliano A E, Kirgan D M, Guenther J M, et al. Lymphatic mapping and sentinel lymphadonectomy for breast cancer. Ann Surg 1994; 220: 391-401
9. Albertini J J, Lyman G H, Cox C. et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 1996; 276: 1818-22
10. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel Node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. Lancet 1997;349: 1864-7
11. Cody HS, Borgen PI. State of the art approaches to sentinel node biopsy for breast cancer: study design, patient selection, technical and quality control at Memorial Sloan Kettering Cancer Centre. Surg Oncol 1999; 8: 8591.

Dr Michael Jensen

Soft Tissue Neoplasms – An Update: Head and Neck Sarcomas – the St Vincent's Experience

Overview

Sarcomas are uncommon malignant tumours, of apparent mesenchymal origin, accounting for 1% of all malignancy. The majority in adults arise within large muscle groups of the extremities; other sites include the buttocks, chest wall, retroperitoneum and head and neck. The relative rarity and morphologic heterogeneity of soft tissue neoplasms render them liable to misdiagnosis and present a significant challenge to pathologists and oncologists. Clear histological distinction from both benign soft tissue tumours as well as the locally aggressive non-metastasising malignancies, is essential to management. Diagnosis is aided by the use of immunohistochemistry and genetic markers, in addition to light microscopy and ultrastructural studies with electron microscopy. Over the period 1985 – 2000, I have documented 83 cases of soft tissue sarcoma of the head and neck treated at St Vincent's Hospital. This experience will be detailed in the second part of this article.

Dr Michael Jensen, MBBS, FRACS, FACS
Visiting Surgical Oncologist
St Vincents Hospital

Non – Sarcomatous Soft Tissue Neoplasms

This section of the article describes a variety of soft tissue neoplasms to be distinguished from sarcomas.

Fibromatoses

Arising in the subcutaneous or deep fascia, an aggressive fibromatosis must be distinguished from a true malignancy.

On CT scanning, a peculiar stranding effect extends from the non encapsulated "tumour" mass. Although seen in limbs or trunk, fibromatoses more commonly present in the head and neck (especially in the soft tissues at the base of the neck or shoulder girdle), occasionally presenting submucosally, e.g. in the bucco-alveolar sulcus. Characterised by local infiltrative growth, a fibromatosis never metastasises. Spontaneous regression has been reported. Often painful, these lesions are treated by simple excision. If surrounding and involving nerves such as the brachial plexus, a local course of radiation therapy may be considered.

The deep fibromatoses include:

(i) abdominal wall and (ii) intra-abdominal desmoid tumours.

The extra abdominal desmoid tumour usually arises in association with

pregnancy, mostly during gestation, commonly from musculoaponeurotic structures of the abdominal wall. Intra-abdominal desmoid tumours may present as a scar-related tumour in Gardener's syndrome, usually arising in the retroperitoneal tissues or mesentery within one to two years of a surgical procedure.[1] Treatment requires surgical excision with a good margin to prevent local recurrence. This is technically difficult when the tumour arises within the mesentery .

Mesenteric and pelvic fibromatoses are closely related variants that seem unrelated to childbirth or gestation and develop spontaneously without prior surgical intervention. Adequate treatment is difficult, often reserved for specific complications.

Dermatofibrosarcoma Protuberans

A difficult low grade soft tissue tumour to treat, this tumour often presents as a skin nodule that microscopically extends eccentrically in the subcutaneous tissues for several centimetres beyond macroscopic tumour. These lesions tend to locally recur. They rarely metastasise, unless associated with frequent recurrence or rare fibrosarcoma transformation. It is usual to attempt at least a 3cm margin around the macroscopic tumour. Some authorities have attempted Moh's surgery to delineate the spread of tumour in combination with frozen section margins.

Atypical Fat Forming Tumours

(a) Subcutaneous:

The "fat forming" liposarcoma or atypical lipoma, commonly arises in the subcutaneous tissues of the posterior neck, upper back or chest. This group of histologically atypical adipocyte tumours reveals variation in adipocytes with nuclear hyperchromasia but is generally lacking in lipoblasts. Recurrence develops if not adequately excised, usually with a favourable clinical course. If not controlled and multiple recurrence occurs, dedifferentiation with aggressive behaviour is possible.

These low grade liposarcomas should be distinguished from the spindle cell and pleomorphic lipomas, which are essentially benign tumours that are pathologically distinct, rarely recur and never progress to metastasis. These lesions have quite different cytogenic abnormalities.

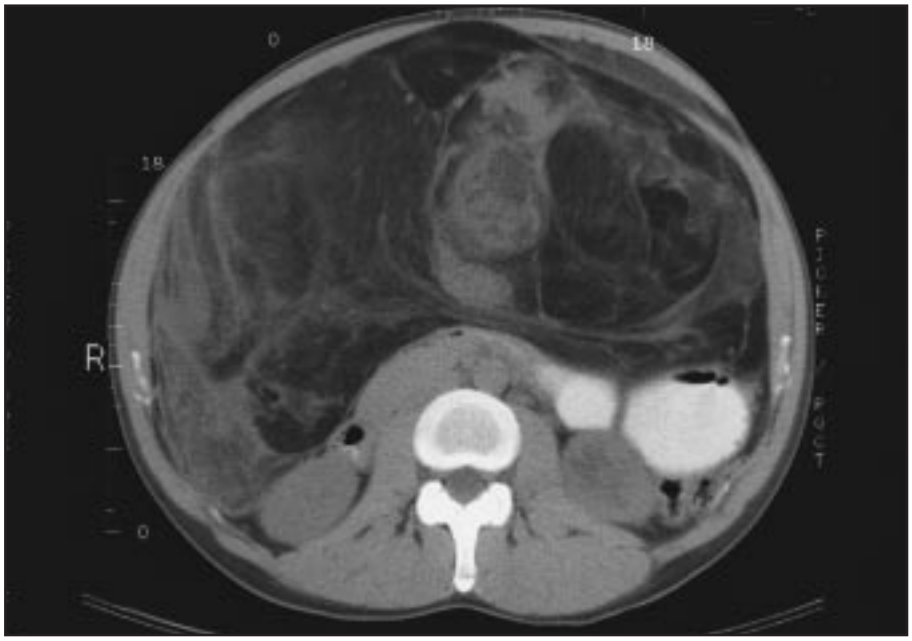


Figure 1a. Fifty year old male with 13kg low grade atypical lipoma of the abdominal cavity. Tumour removed with narrow margins; first recurrence after three years; three further surgical clearances; patient is alive and well after 7 years.

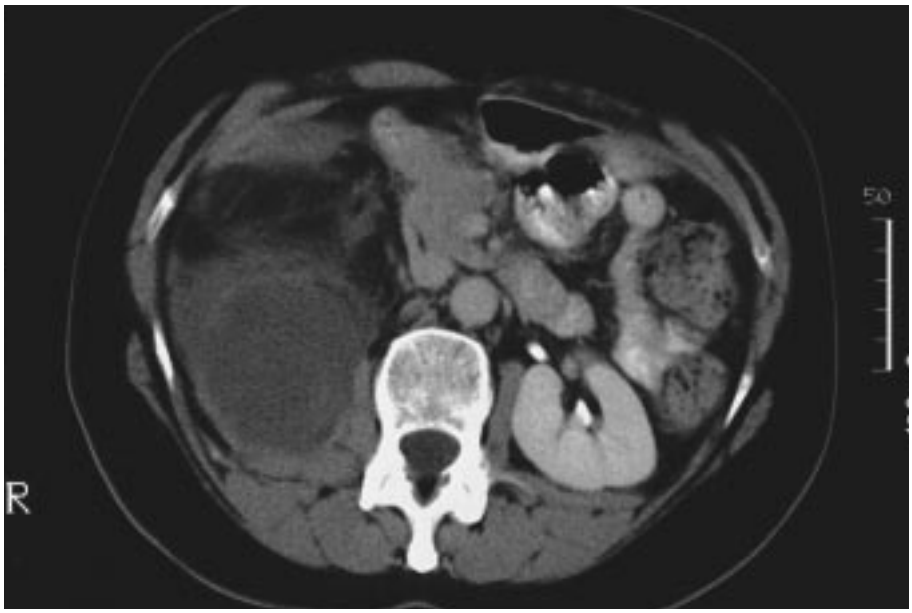


Figure 1b. High grade liposarcoma in a 42-year-old female. Wide excision included right kidney and psoas muscle. Post operative brachytherapy and extended beam treatment. No recurrence at 6 years.

(b) Retroperitoneal/Deep Sites:

Morphologically indistinguishable from the subcutaneous variety but with more aggressive behaviour, these lesions presenting in the deep subcutaneous tissues of the groin, or in the retroperitoneum, issue a considerable challenge. Several studies have demonstrated the potential for dedifferentiation in recurrent well differentiated liposarcomas of deep soft tissue or retroperitoneum.[2,3] In the retroperitoneum, because of the potentially fatal consequences of local recurrences and the relative inability to undertake complete surgical clearance, most tumours will recur and ultimately lead to loss of a life. Low grade "atypical lipomas" occurring in the retroperitoneum may reach a spectacular size "gently" pushing aside normal structures. Tumours from 20-30kgs in size are not uncommon. Repeat resections should be undertaken.

Figures 1a and b show examples of low and high grade intra-abdominal fat forming tumours.

Ossifying Fibromyxoid Tumour

A rare low grade tumour, this typically presents as a slow growing subcutaneous mass in the proximal 1imb

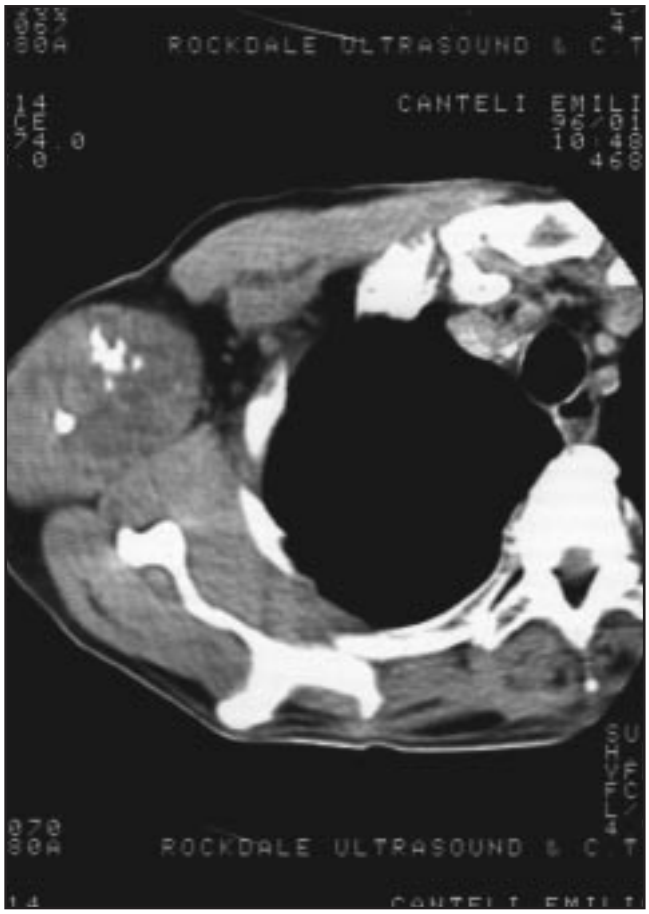


Figure 2 CT scan demonstrating extensive course calcification of a mesenchymal chondrosarcoma.

girdles of adults (male dominant) usually in the fifth to seventh decades. With rare exception, the lesion is solitary and asymptomatic and, if well excised, rarely recurs.[4] These tumours have a dense pseudocapsule with a varying amount of osteoid bone formation.

Fig 2 is a CT scan of a 75 year old male depicting an ossifying neoplasm arising within the right axilla.

Elastofibroma

A degenerative "pseudotumour", this usually arises in elderly patients and manifests as a slow growing solid mass of fibroelastic tissue between the lower portion of the scapula and chest wall. It may reach 5cm to 10cm in greatest diameter. This reactive process is usually attached to the thoracic fascia, periosteum and ligaments of the 7th and 8th ribs.

Infiltrating Angiolipoma

A benign, mixed mesenchymal tumour often mistaken for sarcoma, the infiltrating angiolipoma of skeletal muscle is subdivided into small, large and mixed vessel types. It presents as a painful soft tissue mass, the large vessel variant commonly found in the lower limb, occasionally in trunk and head and neck. This tumour is comparatively more common than the rare angiosarcoma of muscle.

These lesions do not metastasise and pose no threat to life. Surgery on such lesions should be preceded by arteriography and may be associated with considerable deformity and loss of function.[5,6,7]

SARCOMAS

Introduction:

A sarcoma usually presents as a pseudoencapsulated, circumscribed mass. The pseudocapsule contains a mixture of tumour cells, compressed tissue and inflammatory cells with little desmoplastic reaction. With increasing size and tumour grade there is a tendency for seeding of malignant cells along tissue planes of least resistance, including muscle or neurovascular bundles, well beyond the apparent pseudocapsule.

Histological subtypes of sarcoma occur in different age groups. A useful recommendation for the reporting of soft tissue sarcomas was published by the Association of Directors of Anatomical and Surgical Pathology.[8]

The typical paediatric sarcoma is a rhabdomyosarcoma either of the embryonal or alveolar subtype. The embryonal variety (70% to 80%) is particularly chemotherapy sensitive and presents mostly in the head and neck, especially the orbits and paranasal sinuses of young children (birth to 15 years). It also occurs in the genitourinary tract and occasionally the retroperitoneum. In children, where complete remission is not achieved with chemotherapy, the AMORE protocol is used. This protocol describes ablative surgery, moulage technique with brachytherapy and reconstructive surgery.[9]

The alveolar type accounts for 10-20% of all rhabdomyosarcomas and is seen usually in the 10-30 year age group.

Also encountered in the teenage to 30 year age group are synovial, epithelioid and clear cell sarcomas as well as mesenchymal chondrosarcoma and primitive neuroectodermal tumours.

Over 40 years of age, the predominant sarcomas are the malignant fibrous histiocytoma, liposarcoma, fibrosarcoma, leiomyo sarcoma, malignant nerve sheath nerve tumour and pleiomorphic rhabdomyo sarcoma.

The majority of these sarcomas have a similar natural history, present commonly in the periphery, with prognosis largely determined by grading and size.

Recent studies with immunohistochemistry and genetic markers have led pathologists to reclassify pleiomorphic sarcomas usually reported in the forty plus age group. Many formerly regarded as malignant fibrous histiocytomas (M.F.H.), have been deconstructed to now include leiomyosarcoma, liposarcoma and rhabdomyosarcoma. MFH becomes a diagnosis of exclusion but has some identifiable features that set it apart from other pleiomorphic sarcomas.[10,11]

In the elderly, a variety of aggressive angiosarcoma commonly arises in the scalp, unusually may spread to lymph nodes and is invariably fatal with local uncontrolled disease after several years. The tumour presents as a vascular malformation with poorly defined margins often mistaken for simple haemangioma. These lesions will respond to radiation therapy with local control in the treatment field but

inevitable recurrence at the margin. A similar result occurs with surgery.

Primitive Neuroendocrine Tumours

This undifferentiated small, round cell, mesenchymal neoplasm with little evidence of ultrastructural specialisation, is commonly described as an extraskeletal Ewing's sarcoma. These tumours share identical patterns of proto-oncogene expression with Ewing's sarcoma with common expression of the MIC2 gene.[12,13]

Commonly a paediatric malignancy, these tumours present in unusual sites in young adults but fortunately are chemotherapy sensitive. Protocols of treatment involve extensive chemotherapy followed by radical ablative surgery with local radiation therapy and consolidation chemotherapy.

Extraskeletal Chondrosarcoma

An aggressive malignancy with very poor prognosis, the mesenchymal chondrosarcoma typically occur in the15-35 age group. This tumour often presents with a peculiar calcified appearance – a high grade variant of soft tissue sarcoma. Local control may be achieved with radical surgery and radiation therapy. Distant soft tissue and bony metastases are common.[14]

A typical example of mesenchymal chondrosarcoma is shown in Figure 3.

This tumour is to be distinguished from low grade myxoid chondrosarcoma, which when completely excised, has an excellent prognosis with a high degree of permanent local control and smaller risk of metastatic disease, e.g., chondrosarcoma of the larynx, (where 70% arise from the cricoid and 20-30% from thyroid cartilage.[15] Most myxoid extraskeletal chondrosarcomas arise in the deep tissues of the extremities of older patients, usually within the musculature.

Surgical clearance of chondrosarcoma is dependent upon the site of presentation, more difficult when arising in relatively inaccessible sites such as pelvis or orbit.

Leiomyosarcoma

This malignancy requires special mention in two anatomical sub-sites.

Superficial low grade leiomyosarcomas, presenting in the dermis or subcutaneous tissue, are usually cured by wide local excision. Where margins are limited, radiation therapy is added post-operatively.[16]

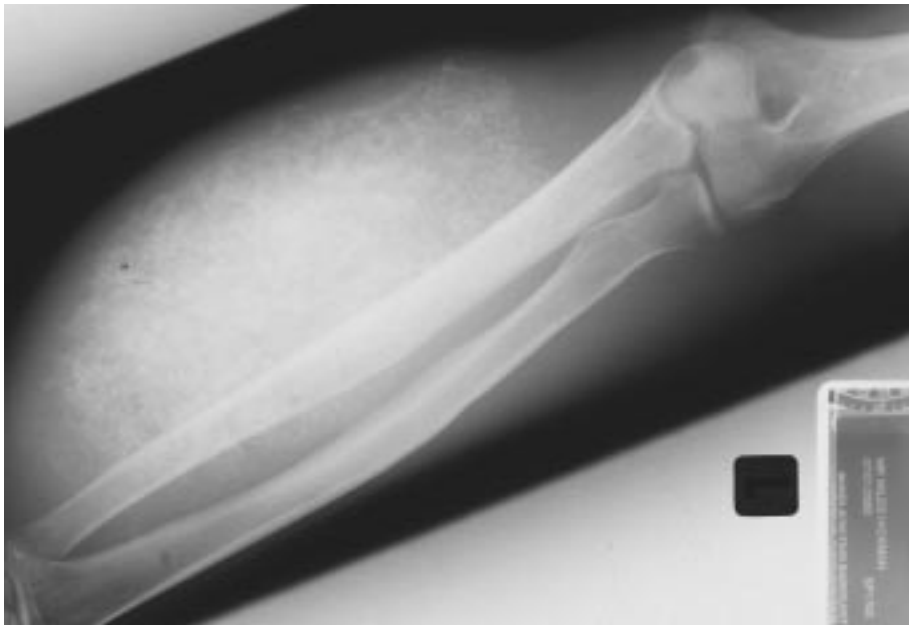


Figure 3 Typical example of mesenchymal chondrosarcoma.

Leiomyosarcoma is the commonly seen aggressive, retroperitoneal malignancy and often invades adjacent structures. It may be possible to effect a radical resection, including the adjacent viscera and, when involved, major vessels such as IVC or aorta, with appropriate vascular reconstruction.

With limited margins, post operative radiation therapy is planned. Refined techniques utilise removable, displacement prostheses to protect small bowel. Brachytherapy is used to supplement conventional external beam therapy.

Leiomyosarcoma also arises from the wall of major vessels, most commonly the inferior venacava (IVC). It may be suprahepatic (a cause of Budd Chiari Syndrome), or infrahepatic – above or below the renal vessels. Infrahepatic IVC leiomyosarcoma is potentially resectable with mobilisation and rotation of the caudate lobe of liver and vascular reconstruction. Limited liver metastasis may occur and does not exclude long term survival.

MANAGEMENT

Diagnosis:

Fine needle cytology of superficial soft tissue tumour facilitates a diagnosis of malignancy and helps rule out melanoma, lymphoma and metastatic carcinoma.

Precise histological typing and grading usually require open surgical biopsy, although this is now possible with image directed core biopsy. Small lesions, say under 2cms, may be excised for histological diagnosis. The majority of tumours will require incision biopsy through a judiciously placed incision. Histopathological difficulty arises where preoperative radiation and chemotherapy were used: this may alter prognostic information, where tumour necrosis is a particular problem.

Treatment:

Surgical resection remains the central theme of management of adult sarcoma in clear distinction to the paediatric sarcomas, where the majority of tumours are first treated with and respond dramatically to chemotherapy, particularly those of round cell type.

Local CT scanning and MRI imaging add considerably to the pre-operative planning and management of sarcomas. Pulmonary CT scanning, to exclude metastatic disease, is undertaken prior to major ablative surgery.

The high local recurrence rate that followed simple excision of high grade tumours led to the development of "soft part" or compartment resection. The principles of this technique, popularised by L Bowden and R Booher in 1958[17], were originally derived from the concepts of George Pack. Where anatomically feasible, this excision includes wide ablation of the malignancy with at least one tissue plane

macroscopically clear of the tumour, including the removal of entire muscle bundles from point of origin to insertion, with sharp tissue plane dissection. The resection encompasses, when necessary, neurovascular bundles. An improved local control rate, up to 75%, is achieved.[18]

As an alternative, and to minimise deformity, radiation therapy is applied to supplement surgery, where deliberately limited surgical margins are applied. A wide "shrinking field" technique of radiation therapy, pre or post surgery, is necessitated to achieve the same high degree of local control possible with "compartment" surgery.

The "shrinking field" prescribes a standard tumour dose of 50Gy to enclose the extended, potential, tumour bed, boosted by higher local peritumour doses and was popularised by Herman Suit.[19] Current limb sparing techniques, with microvascular free grafts for reconstruction, significantly reduce morbidity.

A description of:

a. tumour site and depth – dermal, subcutaneous, intramuscular, retroperi-toneal,
b. type of resection,
c. size of tumour,
d. histological grading and
e. the status of surgical margins:

provide useful information to the surgical oncologist in determining the necessity for adjuvant radiation therapy and/or further surgery.

Amputation is restricted to gross circumferential tumours, particularly where bone invasion is involved. Hemipelvectomy, forequarter and hindquarter operations are limited to relatively rare tumours.

Summary

The vast majority of sarcomas present in the periphery. Using careful planning techniques, especially MRI scanning, a high degree of local control is achieved. The difficult tumours, such as retroperitoneal sarcoma and the high grade relentlessly recurring variants are highlighted.

Although chemotherapy is the mainstay of treatment for paediatric malignancy, its impact in adult sarcomas is minimal with most international studies unable to demonstrate a significant survival advantage for the use of adjuvant chemotherapy. Programs using chemotherapy with high grade sarcoma are currently being evaluated. Modern efforts in adult sarcoma therapy concentrate on clever reconstructive surgery and new techniques of radiation.

In the future, intensity modulated radiation therapy using beams that are modulated during the delivery of the treatment field have great potential for the treatment of sarcomas in relatively inaccessible sites, particularly the head and neck, utilising radiated volumes in a highly contoured fashion and sparing vital structures.[20]

Sarcomas of the Head and Neck: The St Vincent's Experience

In our combined series from the Head and Neck group at St Vincent's, 83 head and neck soft tissue sarcomas were reported in the 15 year period from 1985 to 2000.[21]

This compares with historical data from the New South Wales Cancer Registry, which records 538 patients with the diagnosis of head and neck sarcoma in the 25 year period 1970 – 1995. This includes all soft tissue and bone sarcomas. During the same period, 208 deaths were recorded. There were a small number of paediatric tumours and teenage malignancies with the vast majority of sarcomas arising in the 50 plus age group.

This adult hospital excludes patients under 15. As shown in Fig. 4, there was a clear bimodal distribution of patients in this series.

A significant group, particularly males in the 15 to 30 year age group, presented with the diagnosis of alveolar rhabdomyosarcoma. This group did poorly in spite of aggressive combination treatment with pre-treatment chemo-therapy, surgery and radiation therapy. A local control rate of only 40% at 3 years was achieved.

Compartment excision, as earlier defined, was rarely possible in the head and neck. Low grade sarcomas under 3cms in size were treated by surgical excision alone. This particularly applied to tumours arising in the scalp and neck and included dermatofibrosarcoma protuberans and small superficial leiomyosarcomas.[22]

Topographical data in our series demonstrated the vast majority of head and neck sarcomas involved the soft tissues of the scalp and neck. The different pathological subtypes are shown in Fig. 5. The most common pathology was MFH and angiosarcoma, with a smaller number of leiomyo-sarcoma, pleiomorphic rhab-domyo-sarcoma and dermatofibrosarcoma protuberans. Wide excision and radiation therapy were used for all high grade tumours.[22, 23]

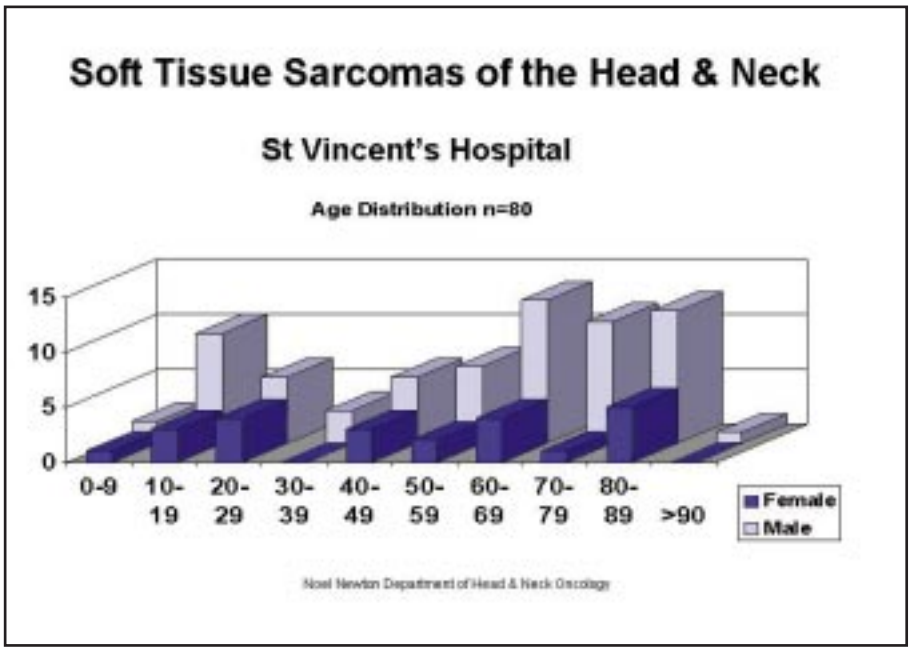


Figure 4

The poorest subgroup were the 10 elderly patients with angiosarcomas, mostly of the scalp and face who demonstrated relentless local recurrent disease. Although temporary infield control could be achieved by wide fields of radiation therapy and surgery, disease inevitably recurred at the periphery of the treatment fields. Many patients developed lymph node metastases, most died with aggressive local behaviour invading orbit, ear canal, oral cavity, etc. Our current therapy for these patients uses wide field conformal radiation therapy to cover a large area of the head and neck, aiming for local control.[24, 25]

Chondro-osseous tumours were an interesting subgroup of 14 patients. The chondro-osseous group were dominated by chondrosarcomas with the largest number involving the cricoid. Most were low grade tumours with an excellent prognosis where complete excision was usually possible.

Conclusion

If we exclude the two poorly behaving groups (the 15-30 year old age group with alveolar rhabdomyosarcoma and the elderly patients with angiosarcoma), the remaining majority (65 patients with head and neck sarcoma) have a similar prognosis to patients with sarcoma arising in the periphery, with a high local control rate approaching 70%.

Our experience concurs with the literature and highlights the heterogeneity of soft tissue neoplasms, as presented in this article. The importance of histological diagnosis and the necessity to distinguish benign soft tissue tumours and the aggressive, locally invasive malignancies has been stressed.

Surgery, either as a stand alone compartment excision or with planned radiation therapy utilising brachytherapy in combination with external beam, remains the most important modality in the management of adult sarcoma.

References

1. Jones I T, Jagerman D G, Fazio V W. et al Desmoid Tumours in Hereditary Polyposis. Ann Surg 204: 94, 1986.
2. Weiss, SW, Rao,VK, Well Differentiated Liposarcoma (atypical lipomatous tumours) of deep soft tissues of the extremities, retroperitoneum, and miscellaneous sites ; a follow up study of 92 cases with analysis of the incidence of dedifferentiation, Am. J.of Surg.Path., Vol 16: 1051 – 1058, 1992.
3. McCormick,D, Mentzel,T, BehamA, Fletcher,CDM: Dedifferentiated liposarcoma; clinicopathological analysis of 32 cases suggesting a better prognostic group among pleomorphic sarcomas, Am. J. Surg. Pathol, Volume 18, 1213 – 1223, 1994.
4. Goodlad J R and Fletcher C D M, Recent Developments in Soft Tissue Tumours, Histopathology 27, 103-120, 1995.
5. Allen P W and Enzinger,FM. Haemangioma of skeletal muscle, An analyses of 89 cases, Cancer 29; 8 – 29, 1972.
6. Dionne G P, and Seemayer T A, Infiltrating lipomas and angiolipomas revisited, Cancer 33, 732 – 738, 1974.
7. Vasantha K Rao ,M D and SharonWeiss, M D. Analysis of Histological Features and Clinical Outcomes in 51 Cases. The American Journal of Surgical Pathology, Volume 16, 764 – 771, 1992.
8. Recommendations for Reporting Soft Tissue Sarcoma. Am.J. Clin. Pathol. 111. : 594 – 598, 1999
9. Schouwenberg P F, Kupperman D, Bakker F P, Blank L E, de Boer H B, New combined treatment of surgery, radiation therapy and reconstruction in head and neck, rhabdomyosarcoma in children, the AMORE Protocol. Head and Neck, Vol. 20, 283 – 292, July 1998.
10. Christopher D.M. Fletcher, Pleiomorphic Malignant Fibrous Histiocytoma : Fact or Fiction? Am. J. Surg. Pathol. 16(3): 213-228, 1992.
11. SharonWeiss and Hiroshi Iwasaki: Pleiomorphic Sarcomas, Current Issues: XXIII Congress of the International Academy of Pathology. Oct 15, 2000. Nagoya Japan, 2000.
12. Ambros I M, Ambros P F, Strehl S et al. MIC2 is a specific marker for Ewing's sarcoma and peripheral primitive neuroectodermal tumours. Cancer; 67, 1886 – 1893, 1991.
13. Stevenson A J, Chatten J, Bertoni F, Miettinen M. CD99 (p30/32mic2) neuroectodermal /Ewing's sarcoma antigen as an immunohistochemical marker. Appl. Immunohistochem. 2; 231-240.
14. Yasuaki Nakashima MD, Krishnan K, Unni , MB, BS, Thomas C, Shives, MD, Ronald G, Swee, MD, David C, Dahlin MD, Mesenchymal Chondro-sarcoma of Bone and Soft Tissue, Cancer 57; 2444-2453, 1986.
15. Stephen Rodrigues, Stuart Miller and Andrew Whyte, Chondrosarcoma Of The Larynx, Aust. J. Otolaryngology. Vol. 4, (1), 47-49, January 2001.
16. I.Dahl and L. Angervall, Cutaneous and Subcutaneous Leoimyosarcoma A Clinical and Pathological Study of 47 Patients, Path. Europe Vol. 9 : 307 – 315, 1974
17. Bowden L, Boohor R J, The Principles and Techniques of Resection of Soft Parts for Sarcoma. Surgery, 44. 963 – 977, 1958
18. El Castro, MD: Steven I. Hajdu, MD: Joseph A. Fortner MD: New York. Surgical Excision Fibrosarcoma of the Extremities. Archives of Surgery Vol. 107, 284-286 1973.
19. Suit H, Mankin H, Wood W, et al: Radiation in the treatment of primary soft tissue sarcoma. Cancer 55, 265 – 67, 1985.
20. Kenny L, Peters L, Roger A, et al Modern Radiotherapy for Modern Surgeon; An Update, ANZ J. of Surg., Vol 72 131 -137, 2002.
21. Sarcomas of the Head/Neck, Jensen et al, in press.
22. Snehal G. Patel ,MS,FRCS, Ashok R. Shaha,MD, FACS, and Jatin P. Shah, MD, FACS, FRCS (Hon). Soft Tissue Sarcomas of the Head and Neck: An Update Am. J. of Otolaryng., Vol 22 (1), 2-18, 2001.
23. Dagher R, Helman L, Rhabdomyosarcoma; An Overview . Oncologist, Vol 4 (1),34-44, 1999.
24. Bullen R, Larson P O, Landeck A E, et al. Angiosarcoma of the head and neck managed by biopsies and radiation therapy, Dermatol. Surg. Vol 24 (10), 1105 – 1110, 1998
25. Veness M and Cooper S. Treatment of cutaneous angiosarcomas of the head and neck. Aust. Radiol. Vol 39 (3), 277 – 281, Aug 1995.

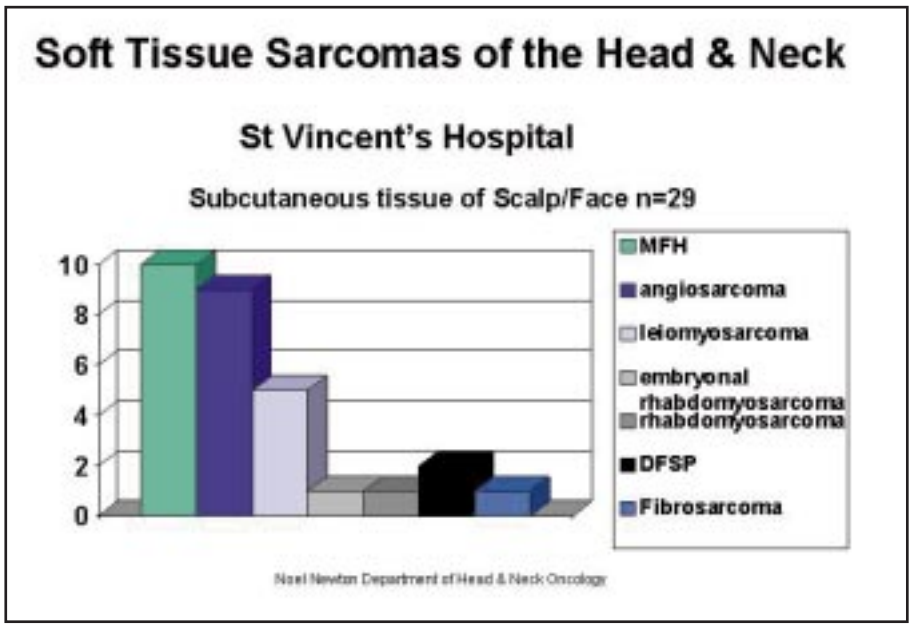


Figure 5

Dr Gordon O'Neill

Diagnosis and Management of Bladder Cancer in 2002

Introduction

The treatment of bladder cancer remains challenging despite significant improvements in preventing disease progression and improving survival. It represents a spectrum from superficial well differentiated disease to highly malignant tumours with a dismal prognosis. Bladder cancer is the fourth most common cancer in men and the eighth most common cancer in women. The overall incidence has increased in developed countries in the last 30 years, yet mortality rates have declined. This is primarily due to the positive impact on disease progression with intravesical immunotherapy.

The median age at diagnosis is 65 and transitional cell carcinoma (TCC) is rarely diagnosed before the age of 40. TCC however has been reported in adolescents and tends to be well differentiated. Males are affected three times more than females. The disease tends to be more aggressive in Afro-Americans and has a higher incidence in cities compared with rural populations.

Tobacco smoking is the most important risk factor, accounting for up to 50% of TCCs. Other risk factors include exposure to polycyclic aromatic hydrocarbons and benzene products found in the dye and leather industry. Hairdressers and painters are at greater risk of developing disease. Cyclophosphamide has been linked to secondary TCC and phenacatin, whilst more commonly linked to upper tract TCC, has been implicated in the development of bladder cancer. There is an unclear association with caffeine and saccharin.

Dr Gordon O'Neill MBBS, FRACS (Urol)
Consultant Urologist
St Vincent's Clinic

Squamous cell carcinoma accounts for 8% of primary bladder malignancies and is usually associated with chronic inflammation. Its incidence is high (up to 30%) in Egypt where schistosomiasis is prevalent. Adenocarcinoma is extremely rare (1-2%) and is usually associated with bladder extrophy or urachal remnants.

Presentation and Diagnosis

Haematuria is the presenting symptom in 90% of patients with bladder cancer and may be gross or microscopic. Other common symptoms include urinary frequency, urgency, loin pain from ureteric obstruction and urinary tract infection. Patients with haematuria, whether macroscopic or microscopic, should be fully assessed with a complete history and physical examination. Urine should be sent for microscopy, culture and cytology. The upper tracts should be assessed with an IVP (Figure 1) and renal ultrasound in preparation for cystoscopy. Tumours found at cystoscopy (Figure 2) are completely resected where possible and random biopsies are necessary if cytology is positive and there is no obvious macroscopic tumour. Following the diagnosis of bladder cancer, other investigations are necessary, such as FBC, UEC, LFTs and chest x-ray. In higher grade and stage disease CT scanning may reveal the extent of local disease, the presence of lymphadenopathy and visceral metastases. Patients with an elevated alkaline phosphatase should also be evaluated with a bone scan. Unfortunately, understaging is common and many patients with locally advanced disease have micrometastatic disease at the time of diagnosis.

Figure 1: Photo of bladder tumour on IVP

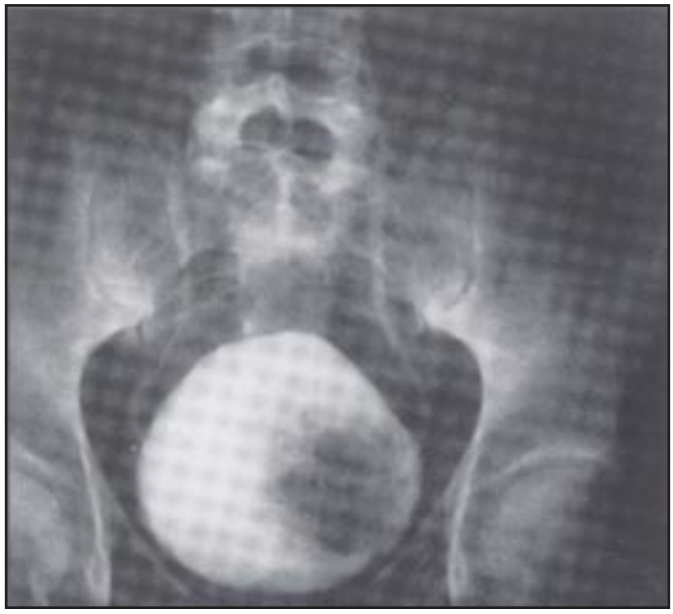
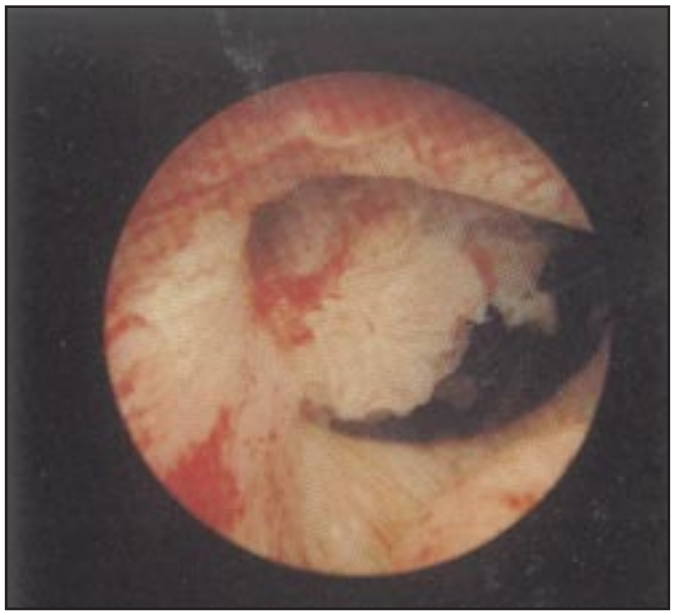


Figure 2: Photo of bladder tumour down cystoscope



Grade and Stage

An understanding of the histological grading and staging of TCC is imperative in its management. Tumours are usually divided into three grades: grade 1 tumours being well differentiated; grade 2 moderately differentiated; and grade 3 poorly differentiated. Grade (G) is particularly important in superficial tumours as a prognostic sign for recurrence and progression. Grade 1 tumours are rarely invasive and most invasive bladder tumours are high grade.

Carcinoma in situ (CIS) is a high grade flat tumour confined to the bladder mucosa which may involve large areas of the bladder. Aggressive treatment is warranted as 54% of patients will have progressed to invasive disease at five years. 5% of patients with CIS will have metastatic disease at the time of presentation.

The most common and useful staging system is the TMN system which was further modified in 1997. The T stages are particularly important, each sub category pertaining to a different prognosis and treatment strategy. TA tumours are confined to the bladder mucosa, T1 have invaded superficially into the lamina propria and T2 tumours are muscle invasive. T3 tumours are now defined as those that extend beyond the bladder to involve the perivesical fat (see Table).

The Natural History of TCC

74% of TCCs of the bladder are superficial at the time of diagnosis. Of these 70% are stage TA and 30% are stage T1. Metastatic disease is found in 5-20% of patients at diagnosis and is usually associated with invasive local disease. Approximately 5% of patients will have upper tract tumours at the time of diagnosis which may increase to 20% within five years. Superficial bladder cancer is usually associated with a defect

of the entire bladder mucosa and as a result recurrences are common. Despite complete tumour resection, two thirds of patients will develop recurrences within five years and 88% by 15 years. Progression from superficial bladder cancer to deep muscle invasion occurs in 15% of patients with regular endoscopic follow up. The natural history of invasive disease treated with local therapy alone results in distant metastases within two to three years in the majority of patients. Metastatic disease is often fast growing and lethal with five year survival rates less than 5%.

The incidence of lymph node involvement in bladder cancer is linked to a number of prognostic factors, stage and grade being the most important: T1 5%; T2 30%; T4 50%. Other prognostic factors include tumour size, tumour multiplicity and the presence of CIS.

Many biological markers have been examined and p53 antigen expression appears to be the most clinically useful. Increased concentration of "wild" type p53 has been shown to predict a significantly increased risk of recurrence and death and may be useful in future to identify a sub population of patients with particularly aggressive tumours who may benefit from adjuvant therapy.

Current TMN Staging for Primary Bladder Cancer, including Modifications made in 1997

Primary Tumour (T)		
Tx	Primary tumour cannot be assessed	
TO	No evidence of primary tumour	
Ta	Non invasive papillary carcinoma	
Tis	Carcinoma in situ	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades (inner half) superficial muscle
	T2b	Tumour invades deep muscle
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades adjacent structures	
	T4a	Tumour invades prostate, uterus, vagina
	T3b	Tumour invades pelvic wall, abdominal wall
Regional Lymph Nodes (N)		
Nx	Regional nodes cannot be assessed	
NO	No regional lymph node metastasis	
N1	Metastasis in a single lymph node, 2cm or less in greatest dimension	
N2	Metastasis in a single lymph node, more than 2cm, not more than 5cm in greatest dimension; or multiple lymph nodes, none more than 5cm in greatest dimension	
N3	Metastasis in a lymph node more than 5cm in greatest dimension	
Distant Metastasis (M)		
Mx	Distant metastasis cannot be assessed	
MO	No distant metastasis	
M1	Distant metastasis present	

Management of Superficial Bladder Cancer

General Overview

The standard treatment of stage TA bladder cancer is complete endoscopic resection with or without intravesical therapy. Intravesical therapy is indicated when there is diffuse bladder mucosal involvement or frequent recurrences. Recurrence rates are related to the grade of the tumour. 80% of grade 3 tumours will have recurred by three years.

Stage T1 bladder cancer is usually managed with transurethral resection and adjuvant intravesical chemotherapy or immunotherapy. Grade is highly significant as 50% of patients with T1G3 tumours will progress to muscle invasive disease with regular follow up. In these patients, consideration should be given to early radical cystectomy before the onset of muscle invasive disease which is associated with a greater incidence of micrometastasis at the time of operation.

CIS should be treated aggressively and is often associated with invasive disease. Ideally, all visibly affected areas should be resected or cauterised, but this is not always possible. The most common agent used to treat CIS is Bacille Calmette-Guerin (BCG).

I will now discuss in more detail intravesical chemotherapy and immunotherapy.

Intravesical Therapy

Intravesical therapy for the management of bladder cancer was introduced in the late 1950s with the specific goals of eradicating existing/residual tumour, preventing recurrence of tumour after complete tumour resection and preventing progression of disease.

The suspected biological behaviour of the patient's tumour remains an important factor in the decision of intravesical therapy. In general, intravesical therapy is not required for grade 1 TA lesions which have a

progression rate of <5%. Multifocal TA disease with or without CIS is a relative indication. Stage T1 disease, irrespective of grade, has demonstrated the biological ability to invade with a reported progression rate of 29%. Intravesical therapy is therefore justified to prevent progression to muscle invasion.

Intravesical immunotherapy is now the first line treatment for diffuse CIS and has replaced cystectomy as the initial therapy. Other relative indications for treatment are multifocal superficial disease, low grade TA disease recurring within two years and persistent positive urinary cytology localised to the bladder.

Prostatic urethral involvement with CIS carries a high risk of progression and intravesical chemotherapy is ineffective in its treatment. The use of BCG following TURP has effectively spared cystectomy in many of these patients. There is no indication for treatment of muscle invasive tumours with intravesical therapy of any kind.

Intravesical therapy may utilise chemotherapeutic or immune modifying agents.

1. Intravesical Chemotherapy

The first intravesical chemotherapeutic agent to become popular in the 1960s was Thiotepa. Due to a high incidence of myelosuppression it has been largely replaced by Adriamycin and Mitomycin C. These two agents have high molecular weights and therefore less systemic absorption and fewer side effects. The net benefit of intravesical chemotherapy over transurethral resection alone is a modest 14% at one to three years. Most studies show an advantage of chemotherapy in the reduction of tumour recurrence for the first two or three years. Long term results, however, have shown that the percentage of patients suffering recurrence at five or more years is just as high. Maintenance chemotherapy has been shown to offer no advantage or perhaps even a disadvantage.

Intravesical chemotherapy does not alter disease progression and is rarely used these days in the management of CIS.

2. Intravesical Immunotherapy

BCG is the most commonly used form of intravesical immunotherapy. It is a live attenuated strain of Mycobacterium Bovis and when instilled into the bladder causes an inflammatory response resulting in stimulation of the immune system based on type 1 and type II responses. BCG has been shown to be superior to all forms of intravesical chemotherapy. Prior exposure to tuberculosis does not preclude the use of BCG. Studies have demonstrated a statistically significant decrease in tumour recurrence rate with BCG, compared with chemotherapy and is highly effective in preventing recurrence of stage 1 and high grade tumours. Additionally, BCG is the only intravesical therapy which reduces tumour progression both in stage and grade. BCG is also the most effective agent in the treatment of CIS with a complete response seen in approximately 70% of patients after six cycles, compared with 50% with intravesical chemotherapy. There is now data to suggest that maintenance therapy with BCG improves long term results, increasing the complete response rate to 84%. Patients, nevertheless, remain at risk for recurrence and disease progression despite treatment. BCG has significantly decreased the cystectomy rate for patients presenting with T1 disease.

Dysuria, frequency and a transient fever are common after each treatment with BCG, but usually resolve in two to three days. Side effects increase with successive treatments and rarely a systemic infection may occur causing pulmonary and hepatic infiltrates (BCGosis). The incidence of BCG sepsis has dropped dramatically after the precaution of not administering BCG after traumatic catheterisation or in the presence of continued symptoms. The diagnosis of BCG sepsis is made by clinical presentation with high fever, chills and hypotension. Treatment is with anti-tuberculous therapy.

Other immunotherapeutic agents are currently being evaluated. Interferons act to mediate immune responses through a number of mechanisms and may have a role in the future.

Keyhole-limpet haemocyanin is a highly antigenic respiratory pigment of the mollusc Megathura cranulata and appears active against CIS with minimal toxicity.

Bropirimine, an oral immunomodulator and Porphyrin-mediated photodynamic therapy are on the horizon.

There are currently no intravesical therapies that have efficacy for SCC, adenocarcinoma or other rare tumours of the bladder.

Treatment of Invasive Disease

The primary treatment of muscle invasive TCC of the bladder is radical cystectomy and urinary diversion. Overall, the five year survival of patients with all forms of invasive TCC is only 50%. Survival rates are much better, however, if the tumour has not penetrated the extravesical fat and is over 80% at five years for stage T2A tumours.

Historically, urinary diversion is achieved with an ileal conduit, requiring an external pouch to collect the urine, similar to a colostomy. Ureterosigmoidostomy is rarely performed these days due to the significant metabolic complications associated with the procedure and the risk of late malignancy.

Continent urinary diversions are now widely utilised and may be in the form of a heterotopic reservoir requiring catheterisation from a small stoma in the abdominal wall or as an orthotopic neobladder attached directly to the urethra. This form of diversion allows for the most anatomic recreation of the urinary system. Continent diversions are associated with a larger complication rate and are contraindicated in patients with chronic renal insufficiency. Relative contraindications include previous bowel surgery and patients who live a long way from tertiary medical facilties. St Vincent's campus has a large experience of orthotopic neobladder which is readily offered to patients fulfilling the selection criteria (see previous article in last issue of Proceedings by Dr P Brenner).

Patients with positive lymph nodes at operation or stage T3 and T4 tumours may be candidates for adjuvant chemotherapy. Some studies have demonstrated a modest benefit, but as yet there is no definite advantage in the use of post-operative chemotherapy. There is no data to support the use of pre- or post-operative radiotherapy.

Bladder Preservation Treatment Options

There has been much interest in alternative ways of treating bladder cancer aimed at bladder preservation. Monotherapy options include limited surgical procedures such as transurethral resection of tumour (TURT) alone and partial cystectomy. Both of these options are only applicable to patients with small unifocal tumours and are not advised as definitive treatment for most patients. Chemotherapy alone, whilst often achieving a complete response in some studies, has been found not to be durable.

Using radiotherapy as monotherapy in bladder preservation includes both interstitial brachytherapy and external beam radiation. Interstitial brachytherapy is suitable for only a small sub-set of patients and when used in combination with external beam radiotherapy is limited to those having tumours <5cm in size.

External beam radiotherapy alone has historically been used as first line treatment in the UK, but is associated with a five year survival of only 20-40%. In addition to the lower survival, cystectomy is required in approximately 20% of patients treated with radiotherapy alone.

The combination of TURT followed by chemotherapy and radiotherapy is associated with higher bladder preservation rates. If the muscle invasive tumour can be completely resected, five year data show survival rates of 5% less than conventional radical cystectomy. The optimal schedule for chemotherapy and radiotherapy has not been determined at the present time but typically a Cisplatin based regimen is used. There is now much data supporting the option of bladder sparing treatments for some patients with muscle invasive tumours, but a direct comparison between it and radical cystectomy has not been carried out.

Treatment of Metastatic Disease

Metastatic bladder cancer is usually incurable and the general approach is palliative. Complete response is <20% and is usually associated with significant toxicity. Newer, less toxic chemotherapeutic agents are now available but unfortunately are no more effective than the traditional agents.

Follow Up of Superficial Bladder Cancer

Regular follow up of stage TA and T1 bladder cancer must be vigilant in order to recognise changes in tumour grade and stage which may lead to the development of insidious muscle invasive disease. Urinary cytology should be collected every three months just prior to cystoscopy and is necessary to exclude the development of CIS.

Cystoscopy is carried out every three months for the first year and if no recurrences are found, every six months for two years and then yearly thereafter. Once a recurrence is found, the patient is placed back on the three monthly protocol.

One major advance in the follow-up of superficial bladder cancer is flexible cystoscopy which can be performed easily under local anaesthesia in the outpatient or office setting. In this way patients only need undergo general anaesthesia when positive cytology or mucosal abnormalities on flexible cystoscopy are discovered.

Conclusion

Bladder cancer represents a broad spectrum of diseases, the majority of which are superficial and may have little impact on patients' survival. Management consists of endoscopic resection and continued surveillance to ensure that progression does not occur or is detected early if it does occur. Intravesical therapy is an important adjunct to the treatment of superficial disease and is based on prognostic factors of the tumour. BCG immunotherapy is a major advance as it is the only agent to decrease disease progression and has decreased the number of patients requiring radical cystectomy.

Radical cystectomy remains the gold standard for muscle invasive disease, however new therapies are emerging, designed for bladder preservation. Metastatic bladder cancer is a highly lethal disease with very few patients surviving beyond two years. Ongoing investigations continue in the area of superficial and muscle invasive disease and will help to determine optimal therapy from the outset. Newer chemotherapeutic agents and different combinations of agents are being evaluated for patients with more advanced tumours.

Dr Raji Kooner

Renal Cell Carcinoma: Overview and Recent Advances

Introduction

Renal cell carcinoma (RCC) is primarily a surgically managed disease. It has multiple potential presenting symptoms and signs. The diagnosis is often made incidentally, most commonly during an ultrasound or CT scan for abdominal discomfort. Surgical treatment can be technically challenging and efforts to treat advanced disease have been at the forefront of medical and surgical oncology. There have been exciting advances in the development of new minimally invasive strategies for the management of patients with localised kidney carcinoma. The advent of laparoscopic surgery has provided new and significantly less morbid surgical alternatives in patients with localised RCC.

Recent advances in immunological forms of therapy involving Interleukin 2 and allogenic stem cell transplantation therapy have provided new hope for patients with advanced RCC. There have also been significant advances in the molecular genetics of RCC.

RCC accounts for roughly 3% of adult cancers. It occurs most commonly in the fifth to sixth decade and has a male/female ratio of 2:1.

Dr Raji Kooner MBBS (Hons) (Syd), FRACS
Urological Surgeon
St Vincent's Clinic
St Vincent's Hospital

Aetiology

The cause of RCC is unknown. Cigarette smoking is the only risk factor consistently linked to RCC. RCC occurs in two forms, inherited and sporadic. There are three forms of hereditary RCC. The most common is clear cell familial kidney cancer. The others are a hereditary form of papillary RCC and RCC associated with Von Hippel Lindau disease. In recent years various tumour suppressor genes and oncogenes have been identified in patients with RCC. These recent advances will potentially lead to better methods for early diagnosis, prevention and potentially also for therapy.

Pathology

RCC's may vary in size from a few centimeters to lesions that fill the abdomen. RCC is classified as clear cell (majority), granular, papillary and sarcomatoid. The clear appearance is due to the presence of cholesterol in the cytoplasm of RCC cells. RCC's are vascular tumours that tend to spread either by direct invasion to the renal capsule into perinephric fat and adjacent structures or by direct extension into the renal vein.

Staging

The classical staging system by Robson is as follows:-

Stage I: Tumour is confined within the kidney parenchyma.

Stage II: Tumour involves the perinephric fat.

Stage IIIA: Tumour involves the main renal vein or inferior vena cava.

Stage IIIB: Tumour involves regional lymph nodes.

Stage IIIC: Tumour involves both local vessels and regional lymph nodes.

Stage IVA: Tumour involves adjacent organs.

Stage IVB: Distant metastases.

This system is conceptually straightforward but does not account for the generally good prognosis of patients with renal vein thrombosis in the absence of true vein wall invasion. These patients have an approximate 60% five year survival rate.

Clinical Findings

RCC's are the great masqueraders amongst the more common neoplasms. They are associated with a wide variety of presenting signs and symptoms. The classically described triad of gross haematuria, flank pain and a palpable mass occur in only 15% of patients. The majority of patients are detected incidentally. RCC is associated with a wide spectrum of paraneoplastic syndromes including erythrocytosis, hypercalcaemia, hypertension and non metastatic hepatic dysfunction.

Imaging Studies

CT is the current gold standard used in the assessment of renal masses. A typical finding is a mass that becomes enhanced with the use of intravenous contrast material (Figure 1). An IVP used alone is only 75% accurate and hence only performed in selected cases. Ultrasound examination is a non invasive, relatively inexpensive investigation that is useful in determining whether a mass is cystic or solid in nature. Renal angiography is rarely required but may be useful in specific clinical situations, for example guiding the operative approach in a patient with a RCC in a solitary kidney when attempts to perform a partial nephrectomy may be indicated. Magnetic resonance imaging (MRI) is equivalent to CT for staging of RCC. Its primary advantage is evaluation of patients with suspected vascular extension. Fine needle aspiration of primary renal cell masses is rarely performed.

Differential Diagnosis

The majority of solid lesions in the kidney are RCC's. The differential diagnoses include complex cysts, angiomyolipomas, oncocytoma, lymphoma and metastatic lesions.

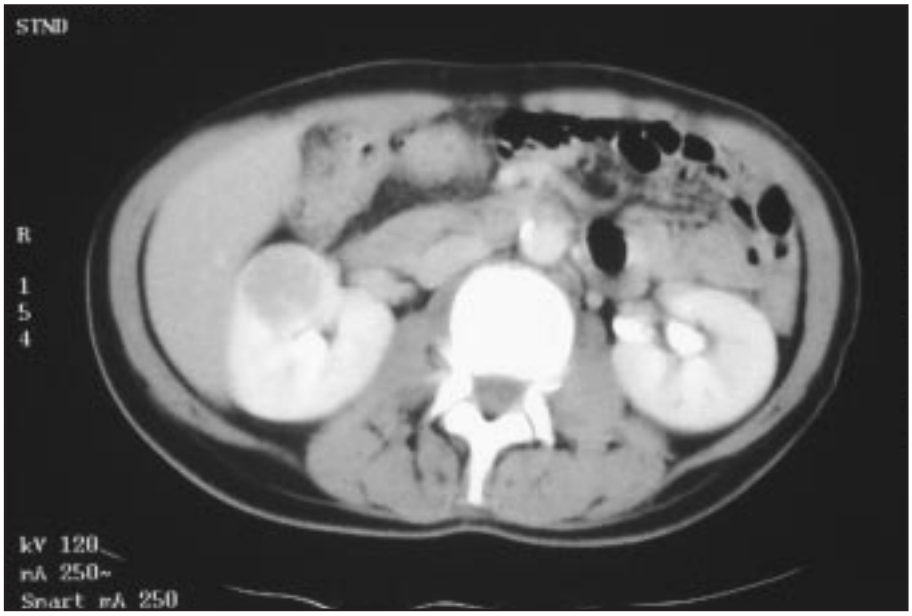


Figure 1. 5cm right renal cell carcinoma

Treatment

(i) Localised Disease

Surgical removal of the early stage lesion remains the only potentially curative therapy available for RCC patients. Appropriate therapy depends almost entirely on the stage of the tumour presentation and therefore requires a thorough staging evaluation.

Radical nephrectomy is the primary treatment for localised RCC. Its goal is to achieve the removal of the tumour and to take a wide margin of normal tissue. Various incisions provide optimal access for the radical nephrectomy.

These include:-

1. Anterior subcostal
2. Thoraco-abdominal
3. Midline
4. The classic flank incision

The role of regional lymphadenectomy in RCC remains controversial. Pre-operative renal artery embolisation is very occasionally used in patients with large tumours in which the renal artery may be difficult to reach early in the procedure. 5% of patients with RCC will present with inferior venal caval involvement. Aggressive therapy is warranted if there is no evidence of metastases. Occasionally the use of cardio-pulmonary bypass is required to resect extensive caval thrombi.

Laparoscopic Radical Nephrectomy (including personal experience)

Laparoscopic radical nephrectomy has been a major recent advance in the surgical management of RCC (Figures 2a – f). The five year cure rate has been similar to open nephrectomy. The major and minor complication rates are similar between open and laparoscopic surgery. Although laparoscopic surgery may require a slightly longer operating time there are significant benefits to the patient with a decrease in blood loss, post-operative analgesic requirements, hospital stay and time to return to normal activities when compared to open radical nephrectomy.

The author presented his initial experience with laparoscopic nephrectomy at a podium presentation of the Royal Australasian College of Urology Annual Meeting (2001). The mean blood loss for the first 22 procedures was 200 ml, median operating time 3.1 hours with a median hospital stay of five days. Most patients were back to work and active within two weeks. There were no major complications and with a mean follow up of eighteen months there has been no tumour recurrence. This cohort of experience demonstrates that good results are achievable with significant benefit for the patient in terms of length of stay and initial recovery. Laparoscopic nephrectomy is now the treatment of choice in the author's hands for patients with localised RCC.

Partial Nephrectomy

Partial nephrectomy is an acceptable form of treatment in patients with a solitary kidney or renal impairment. Recent studies have shown that even for patients with a normal contralateral kidney and a single lesion of 4 cm or less, partial nephrectomy has a similar outcome to radical nephrectomy.

Other Approaches

Observation is a reasonable treatment in elderly patients with tumours of less than 3 cm in diameter. The risk of metastases of a RCC prior to reaching this size is exceptionally low.

Two recent advances in the treatment of localised RCC include the use of radiofrequency ablation (RFA) and cryotherapy. Both forms of treatment can be applied percutaneously, laparo-scopically or via open surgery. Cryotherapy results in the tissue freezing to minus 20 degrees and RFA heats the tissue to 60 and 70 degrees. Both therapies cause cell death. Whilst these therapies are at a very early stage of development they hold significant promise as a minimally invasive potential treatment for RCC.

(ii) Disseminated Disease

RCC is one of the few tumours that demonstrates spontaneous regression in a small number of patients. There is hence an enormous amount of research into the use of various agents such as biologic response modifiers.

A – Surgery

There is little evidence to support the role of nephrectomy in inducing spontaneous regression of metastases. Radical nephrectomy is used as a palliative procedure in patients with severe haemorrhage, unremitting pain and occasionally in the management of paraneoplastic syndrome. Patients presenting with a solitary metastatic site that is amenable to surgical resection may be candidates for combined nephrectomy and removal of the metastatic focus. In carefully selected patients the five year survival has approached 30% in some series. The role of nephrectomy as a means of reducing tumour burden prior to the administration of biological response modifier therapy and the more recent use of adjuvant nephrectomy in patients with evidence of clinical response to biological response modifier therapy, remain controversial and the subject of ongoing clinical trials.

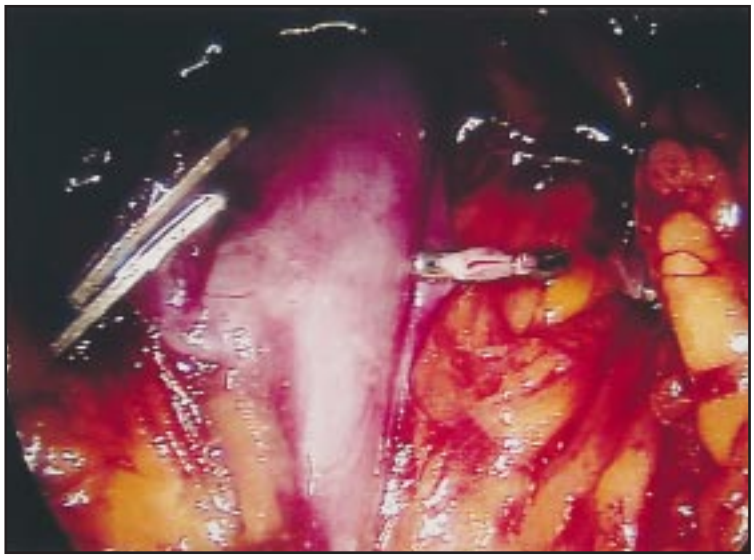


Figure 2a. Laparoscopic nephrectomy. Renal vein exposed with adrenal and gonadal veins clipped.

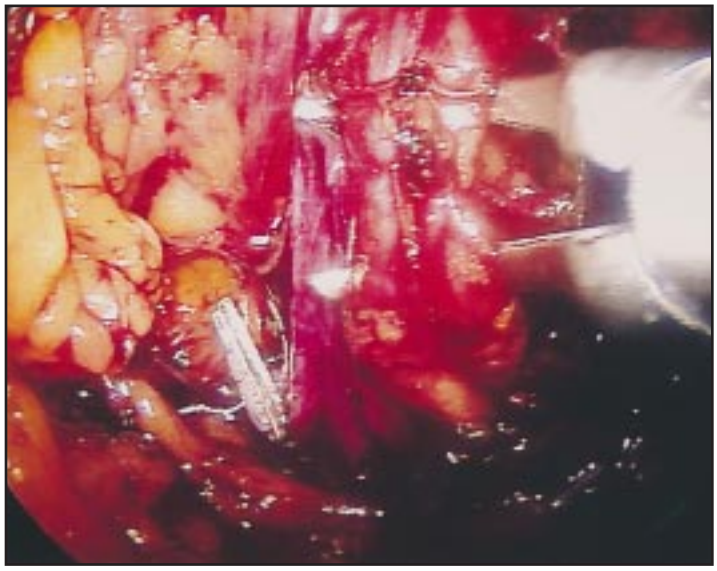


Figure 2b. Renal artery exposed.

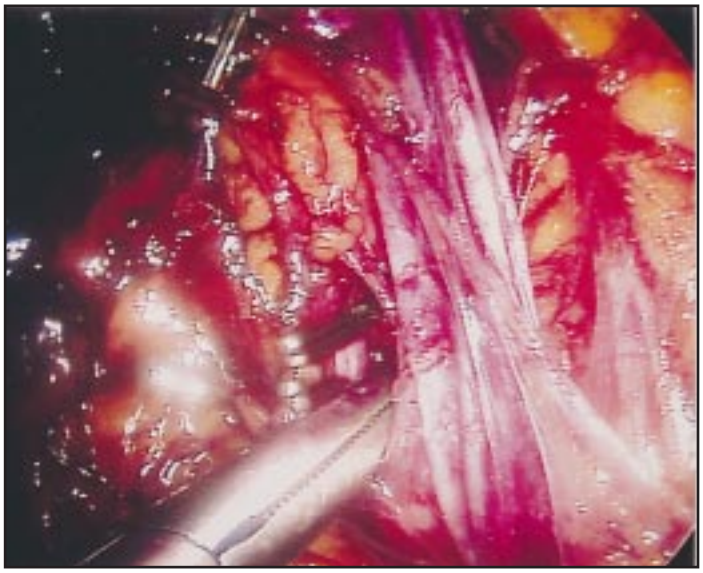


Figure 2c. Renal artery clipped.

B – Radiation Therapy

RCC is a relatively radio-resistant tumour. This, however, can provide effective palliation of metastatic disease.

C – Hormonal Therapy

Recent studies have shown poor response to the use of progestational, androgenic and anti-oestrogenic agents.

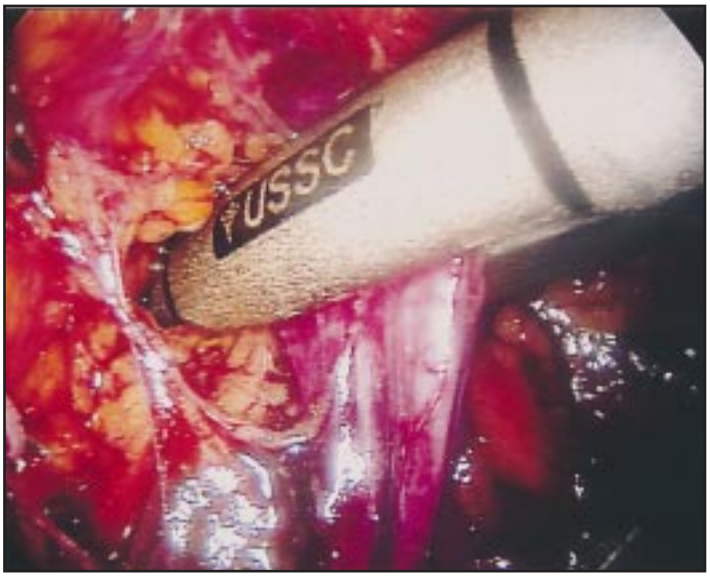


Figure 2d. Renal vein stapled.

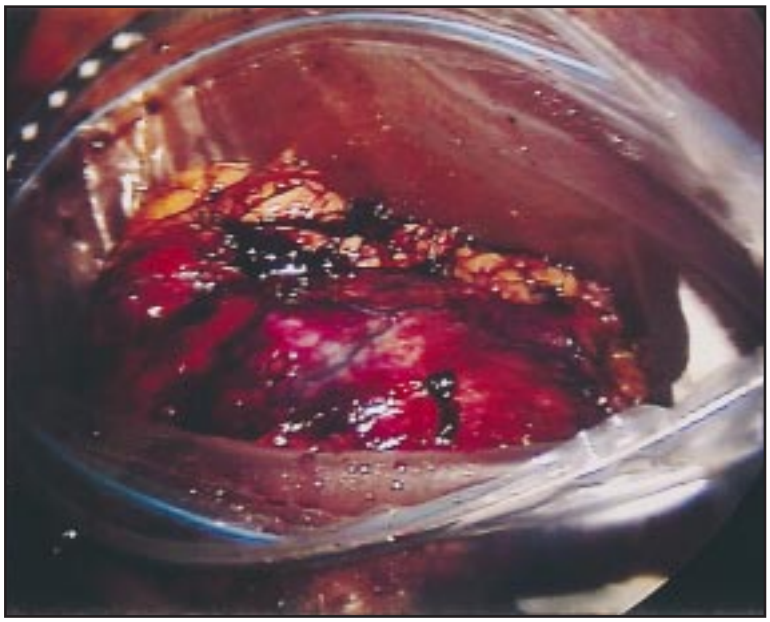


Figure 2e. Tumour in entrapment bag.

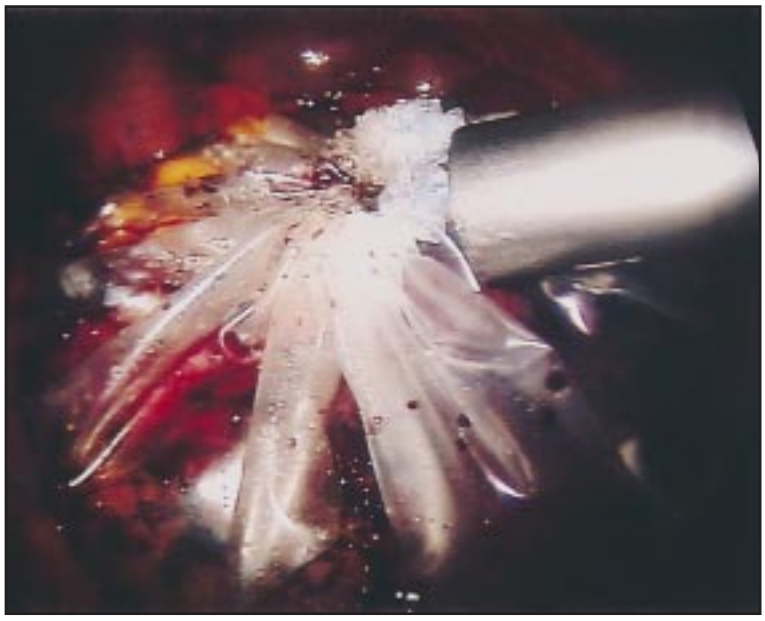


Figure 2f. Tumour enclosed in entrapment bag.

D – Chemotherapy

RCC is amongst the most chemotherapy resistant epithelial cancers. Recent studies have shown response rates of less than 10% and hence chemotherapy is rarely used in patients with RCC.

E Biological Response Modifiers

The use of metastatic RCC as a model for the investigation of various biologic response modifiers is a consequence of both the lack of effective therapy and the long term recognized biologic "eccentricities" of this tumour. The rare phenomenon of spontaneous regression of metastatic RCC has led many to believe this phenomena to be immunologically mediated. A variety of clinical approaches to the immunotherapy of RCC have been tested. Recent agents used include interferons (alpha, beta, gamma), adoptive cellular therapy with tumour infiltrating lymphocytes, auto-lymphocyte therapy and Interleukin-2 (IL-2). IL-2 is the only approved agent by the US Food and Drug Administration office for the treatment of metastatic RCC. It is a cytokine produced by activated T cells that has considerable immunostimulatory and antineoplastic activity. Some studies have demonstrated a 10% complete and a 9% partial response rate (total 19%) with the use of IL-2. Recent data has shown an improved outcome when radical nephrectomy is combined with the use of IL-2 as opposed to the use of IL-2 alone in the metastatic setting.

Prognosis

Patients with RCC who are found to have disease when it is localised to the kidney can have up to a 95% five and ten year survival rate. Patients with renal vein thrombosis in the absence of true vein wall invasion carry an approximate 60% five year survival rate. Those who present to their urological surgeon with locally advanced disease may have a 65% chance of surviving five years. Patients who present with advanced disease have a 20% two year survival rate.

Summary

There have been exciting advances in the development of new minimally invasive strategies for the management of patients with localised kidney cancer. The advent of laparoscopic surgery has provided new and significantly less morbid surgical strategies for the management of patients with RCC. Recent advances in immunological forms of therapy have provided new hope for patients with advanced RCC.

Dr Ian Cole

Laryngeal Cancer – Increasing Role for Conservation – An Overview

Introduction

Laryngeal cancer can be considered to have one of the better prognoses when compared to other cancers of the upper aero-digestive tract (UADT). The five year relative survival rate was 68.2% for males and 61.8% for females in NSW between 1980 and 1995. Two thirds of tumours arise in the glottis (vocal cord) and many present early due to the change in the quality of the voice. This is in contrast to the much poorer prognosis of the anatomically closely related and relatively "silent" tumours of the laryngo (hypo) pharynx. Cancers in these two areas make up about one third of all mucosal cancers in the head and neck. Unfortunately overall survival has not changed in the last 20 years, however the quality of life has certainly improved due to better speech rehabilitation after laryngectomy and as a result of new laryngeal conservation surgery. A combination of chemotherapy and radiotherapy has also been shown to reduce the number of patients requiring a total laryngectomy in carefully selected cases.

Dr Ian Cole FRACS, FRCS
Otolaryngologist Head and Neck Surgeon
St Vincent's Hospital

Anatomy

Although we associate the larynx with speech, its prime function is as the protector of the lower airway, especially while swallowing. It has the appearance of a "ship's ventilator" protruding backwards into the hypopharynx (Figure 1). The lateral food channels or pyriform sinuses pass on each side of the larynx to meet the postcricoid area and eventually the oesophagus.

The larynx is divided for embryological and anatomical reasons into three parts. The Supraglottis, with an abundant lymphatic drainage, is separated from the Glottis (vocal cords) by a space known as the ventricle (Figure 2). It includes the whole of the epiglottis, aryepiglottic folds and its underlying ligament and the false cords. The Glottis begins at the lateral extent of the ventricle (Figure 3) and extends down to 1cm below the free edge of the vocal folds. The Subglottis extends from this point to the lower border of the cricoid cartilage.

The hypopharynx is intimately related to the larynx and cancers of this area can spread to directly involve the larynx or invade via the paraglottic space (Figure 4).

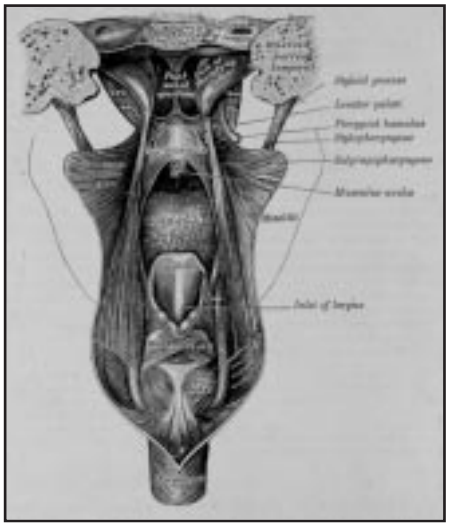


Figure 1. The inlet of the larynx

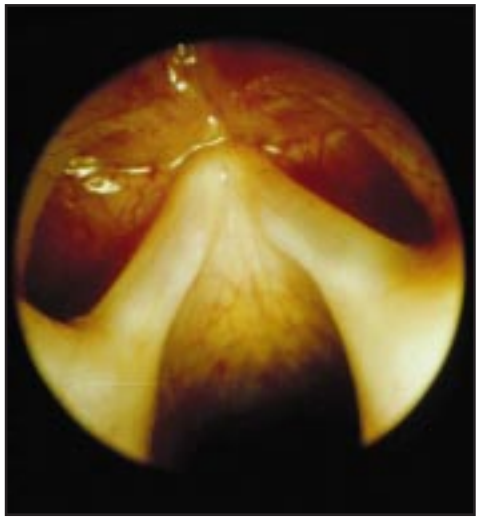


Figure 2. The vocal folds and ventricles seen with a 70 degree telescope

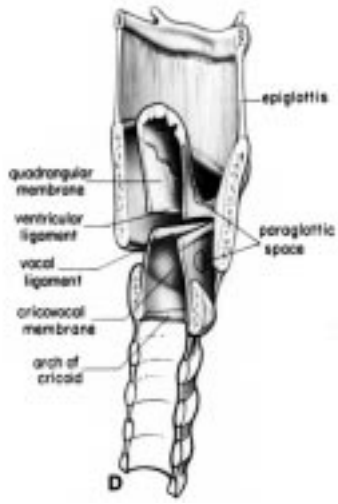


Figure 3. Larynx bisected in coronal plane, demonstrating the ligaments and paraglottic spaces

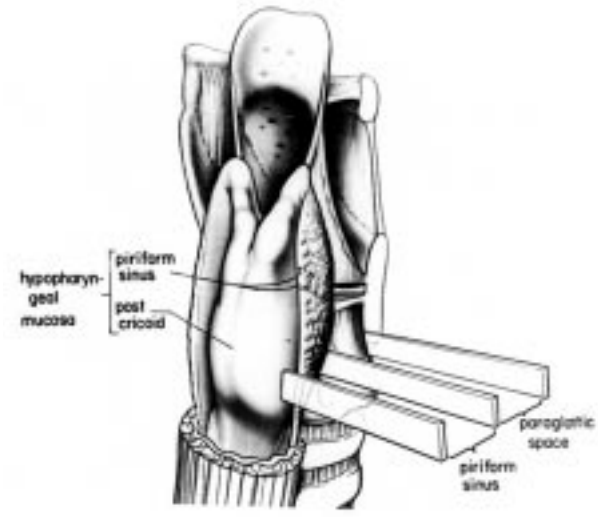


Figure 4. The relationship of the pyriform sinus and the postcricoid area to the larynx. (The former occupies the posterior half of the paraglottic space.)

Table 1. Geographical variation in prevalence of Laryngeal cancer (per 100,000 males only)

HIGH RISK		LOW RISK	
Thailand	18.4	USA (Whites)	6.7
France	17.6	UK	4.9
Italy	16.0	Australia	1.9 – 3.7
Brazil	15.8	Singapore	1.9
India	14.5	Japan	0.6
Spain	13.3		
USA (Blacks)	10.6		

Table 2. Incidence (%) of anatomical sites of cancer within larynx and hypopharynx (1986-2001). Multiple sites indicate difficulty determining site of origin due to the large size of the cancer. (Personal series)

Larynx		
Glottis	- 252	(63%)
Supraglottis	- 127	(31%)
Multiple sites	- 15	(5%)
Subglottis	- 3	(1%)
Hypopharynx		
Pyriform Sinus	-110	(76%)
Post.Pharyngeal Wall	- 15	(10%)
Postcricoid	- 13	(9%)
Multiple sites	- 7	(5%)

EPIDEMIOLOGY

Cancer of the larynx occurs more commonly in the sixth and seventh decade of life.

The male / female ratio used to be 10/1 but, after 1960, there was a noticeable increase in incidence in females so that the present ratio is more like 5/1.[1]

The incidence is approximately 1/10th that of lung cancer. For males this is 4 to 5 per 100,000 for laryngeal and 1 per 100,000 for hypopharyngeal cancer.

It is significantly associated with both cigarette smoking and alcohol abuse. There is also a higher risk in those exposed to fossil fuel burning individual stoves and in blue collar workers in the construction and textile industries.[2]

There is quite a marked geographical variation (Table 1). Australia can be considered a low risk country.[3]

Presentation

Clinical presentation and ultimate prognosis depends very much on the site of origin within the larynx. Glottic cancer presents early with hoarseness, whereas in the supraglottis, sore throat is more likely. The ratio favors the glottis (2/3), although this is reversed in those European countries with a high incidence of UADT tract cancer.

A clinically fixed vocal fold may indicate spread across the ventricle as shown in Figure 5.

In pyriform sinus cancers, which make up 85% of those involving the hypopharynx, sore throat usually progresses over a period of months to dysphagia . Examining the records of 37 cancers at this site from the St. Vincent's Hospital department of Radiation Oncology show a mean period of 122 days or 4 months (median 60 days. SD.112) for symptoms before a diagnosis was made.

The relative incidence of involvement of the different sites within the larynx and hypopharynx in a personal series over a twenty year period is shown in Table 2. Stridor and referred pain to the ear are late symptoms. Metastatic spread to the lymph nodes is unusual in glottic cancer (10-40%), whereas it is 40-50% for supraglottic cancer and 60-70% for pyrifom sinus cancer.

Clinical Tumour staging is shown in Table 3.

Historical Facts

History may have taken a different turn if certain events that eventually led to the death of Crown Prince Frederick (III) of Germany in 1888 could have been averted. The Crown Prince, son of Emperor William I of Germany, married Queen Victoria's eldest daughter, Princess Victoria in 1857. He was a liberal, peace loving and enlightened monarch who was a great anglophile. Unfortunately he died of laryngeal cancer after only 90 days in office, blighting the hopes of every lover of liberty in Europe.

In May 1887, Morell Mackenzie, an eminent laryngologist practicing in London, was asked to provide a second opinion. He performed multiple biopsies under local anaesthetic and had them examined by an equally eminent pathologist, Professor Virchow. The diagnosis of cancer could not be confirmed and, on Morell Mackenzie's recommendation, external surgery (Laryngofissure) was postponed. Eventually a tracheotomy became necessary two months before he died. Germany came under the control of William II, an immature and impatient man, who was brought up in the Prussian imperialist mould. The non-aggression treaty with Russia lapsed and in August 1914 World War I started.

The first total laryngectomy (TL) was carried out by Theodore Billroth in 1837, however survival statistics were abysmal. In a series of seven TL carried out by The Crown Prince's personal laryngologist in Germany, Professor Von Bergman, no patient survived.

It is interesting to speculate what the Crown Prince's survival might have been considering his father lived to over 90 and his son, William II to 82.[4]

Glottic Cancer

Survival rate in early (Stage 1/11) cancer involving just the vocal cords (glottis) is extremely good, being 90% at 12 months and over 80% at 36 months. For stage T1 (mobile vocal cord) local control rate with primary radiotherapy

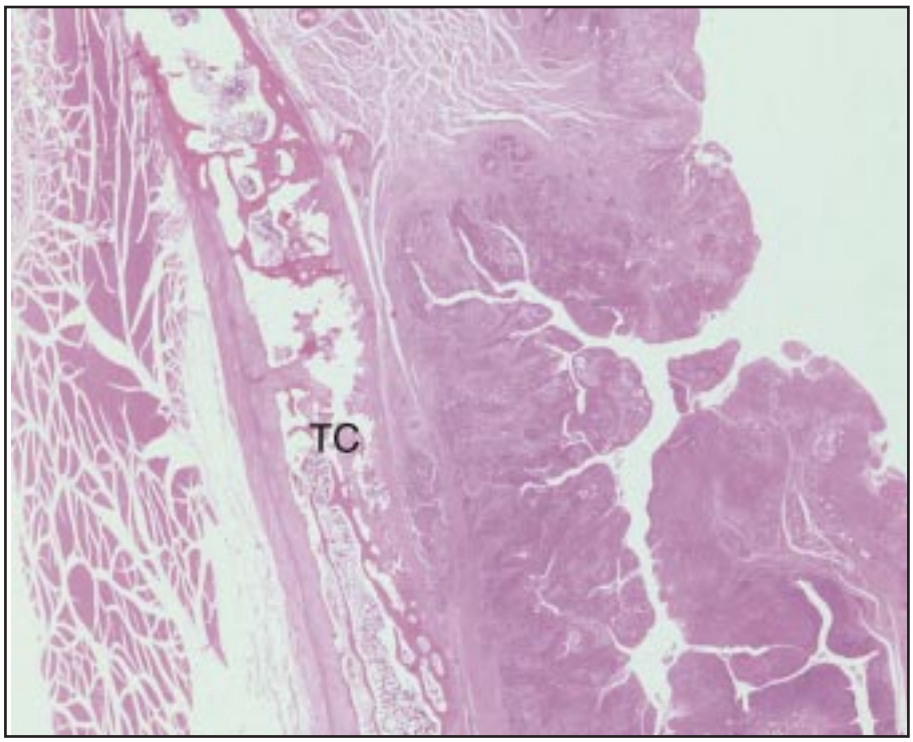


Figure 5. Transglottic cancer (vertical H& E section). Cancer extending across the ventricle but not invading thyroid cartilage (TC).

Table 3. T staging of Laryngeal (and Hypo-pharyngeal) Cancer at presentation (International Union Against Cancer, Fourth Edition)

T1 Vocal fold fully mobile (one subsite)
T2 Impaired VC mobility (or two subsites)
T3 Vocal fold fixation
T4 Through cartilage (or outside region)

and surgical salvage is 96-100%. For stage T2 (reduced mobility or extension to subglottis), it is 52-76%.

Local control is so good because the lymphatic supply of the glottis is poor and cancers remain within the confines of the thyroid cartilage.

Early cancer (stages 1 and 11) is treated with a single modality, i.e. radiotherapy or conservative surgery whereas advanced tumours (stage 111 and 1V) are managed with supracricoid (Conservation) or total laryngectomy followed by irradiation.

Supraglottic Cancer

These cancers are less likely to invade the thyroid cartilage but can spread through the epiglottis to invade the pre-epiglottic space.

Because of the rich lymphatic supply of this part of the larynx, spread to the cervical lymph nodes occurs in almost 50%. Management therefore should include treatment of the neck bilaterally, followed by radiation therapy for patients with spread of cancer into lymph nodes.

Local control with organ conservation, either using partial (supraglottic) laryngectomy, laser surgery or a chemotherapy/radiation protocol also give excellent results and loss of the whole larynx can be avoided in many patients (see below).

The overall 2-year survival rate regardless of staging is 50-69%. Survival with and without neck disease is 46% and 84%, respectively. Only 30% of patients with extracapsular nodal spread survive 2 years.[7]

There is no appreciable difference in survival rates reported from around the world, which are 56%-69%.[8]

Pyriform Sinus Cancer

Two thirds of cases of pyriform sinus cancer present in stages 3 and 4 and have already invaded the larynx. Unrecognized submucosal spread occurs in almost 60%.[9]

Because of the high incidence of associated co-morbidity and second primary cancers, the survival of these patients is poorer than any other site in the head and neck (Figure 6). It is therefore even more important to try to improve the quality of life by larynx conservation in these patients.

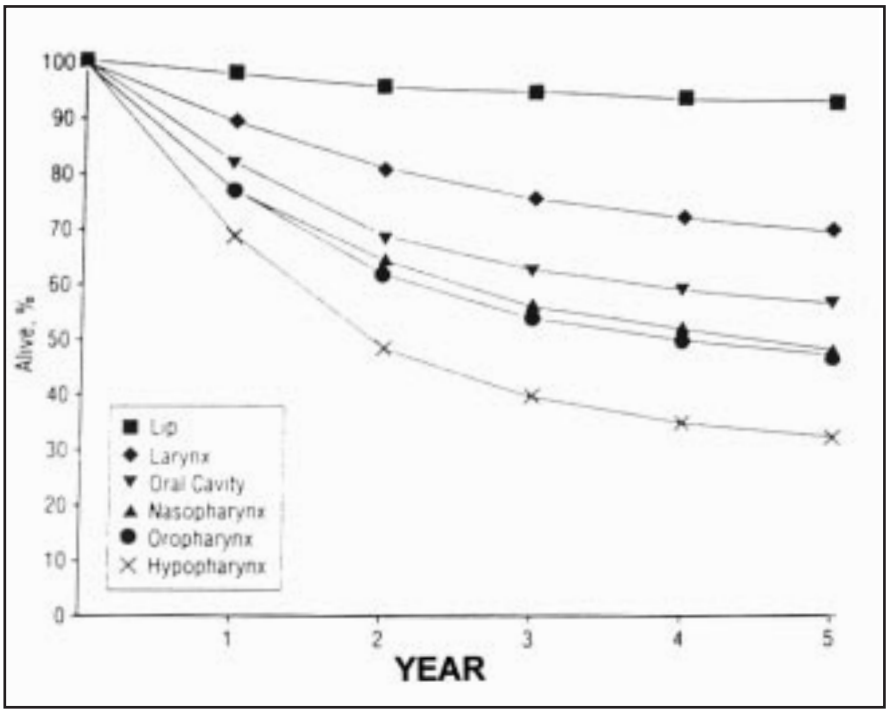


Figure 6. Five year disease specific survival by site (mucosal surface of aerodigestive tract).

Theile et al (Brisbane) popularized the total laryngo-pharyngectomy and replacement with a free flap using an enteric graft such as jejunum.[10] A tubed radial forearm skin flap can also be used, however it is better as a patch graft when some pharynx has been spared.

Voice Rehabilitation Following Total Laryngectomy

Even at the first total laryngectomy by Billroth his associate, Gaussenbaur had designed an instrument to allow air to by-pass the removed larynx, however it relied on preserving an opening into the pharynx (pharyngostome) to allow air to enter and vibrate the pharyngeal muscles.

Success was finally achieved on a reliable basis only in 1982, when Blom and Singer[11] and Panje[12] first introduced the tracheo-oesophageal puncture (TOP). It allowed a one way valve to be inserted from trachea to the pharynx and air could be driven through to vibrate the repaired crico-pharyngeal muscle. This proved to be successful in over 70% of laryngectomies.[13]

Initially TOP's were carried out as a secondary procedure but they are now increasingly inserted at the time of surgery.

It was recognized that 40% of patients were unable to obtain a good voice due to crico-pharyngeal spasm. This has been corrected by myotomy and/or pharyngeal plexus neurectomy, which enables the muscle to relax. Hand free tracheal stoma valves now allow for speech without blocking the stoma with thumb or fingers (Figure 7). The trend is to use long stay valves, which can be in place for many months without changing. Hopefully in the future an anti-fungal agent will be incorporated to prevent deterioration from Candida impregnation.

Larynx Conservation

Induction chemotherapy

No benefit in survival has been achieved by addition of chemotherapy, however the results of induction chemotherapy (Cisplatinum and 5 Fluorouracil) followed by definitive radiation therapy were compared to those of conventional laryngectomy and postoperative radiation.

This study by the Department of Veteran Affairs Laryngeal Cancer Study Group has shown that in advanced (Stage 111/1V) laryngeal cancer, 2/3 (64%) of larynges could be saved.[14]

In pyriform sinus cancer, less spectacular results were achieved. Three and five year estimates for laryngeal preservation were 42% and 35%.[15]

Our protocol is to use the neoadjuvant organ preservation treatment for stage 111/1V supraglottic and some transgottic cancers providing there is no radiological evidence for cartilage invasion.

Conservation Surgery

Transoral CO2 Laser surgery.

This surgery has become increasingly popular over the last 5 years because of the low morbidity and short hospital stay compared to conventional external surgery. Often tracheotomy is avoided. Steiner from Goettingen, Germany has popularized this surgery and introduced the concept of sectional removal of large tumors by cutting across and removing them in segments rather than attempting to laser around them (16,17). For early glottic cancer, survival was 96.7% and local control 85.8% .It is contraindicated when the framework of the larynx is invaded.

Three year recurrence free and overall survival rate for early supraglottic cancer is 87% and 85%, respectively.

It is a safe and time and cost-effective alternative to both external excisional surgery with planned post-operative definitive radiation and, in some cases, radiation alone.

External conservation surgery

Surgical conservation includes partial laryngeal surgery (supraglottic and vertical hemi-laryngectomies), popularised in the 1960's and still in use today and the more recently described supracricoid procedures for previously unresectable disease.

Early glottic cancer that invades cartilage on CT is best treated with one of the vertical partial laryngectomies. It is also a successful procedure for salvage after radiation failure. No evidence of disease rate at two and three years was 85% and 73%, respectively, with ultimate local control of 72% (median of 5.75 years) in a consecutive series of 21 patients.[19]

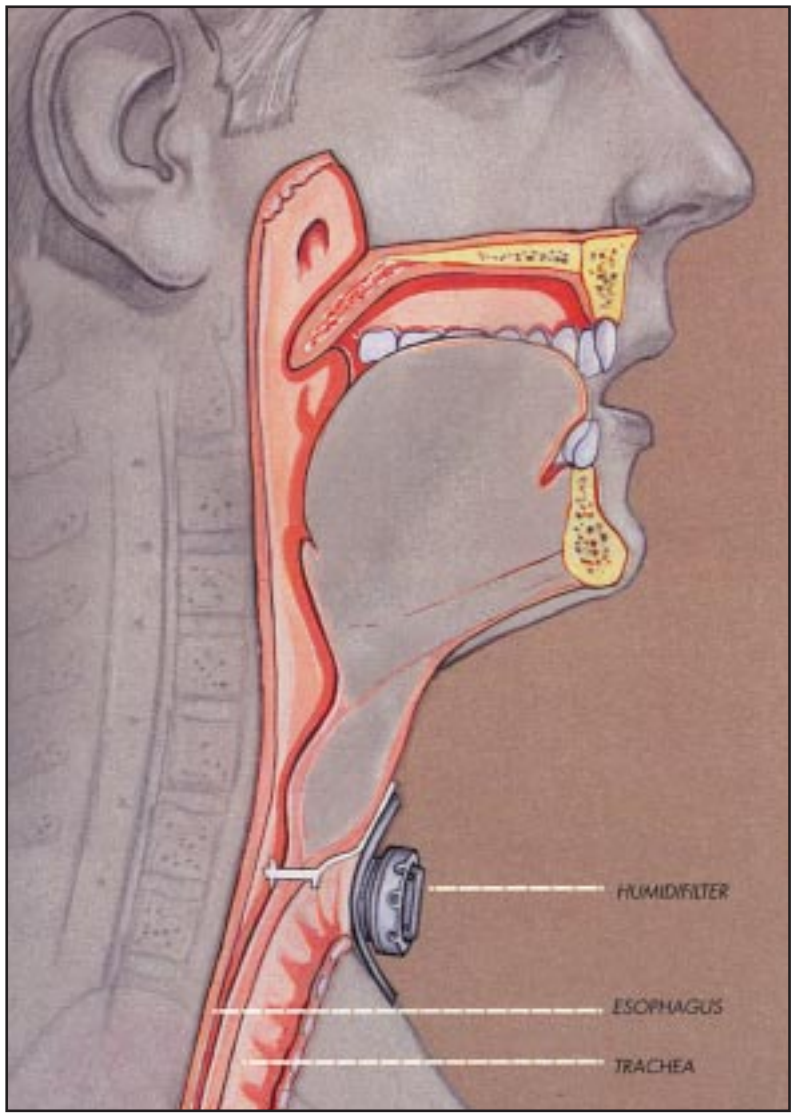


Figure 7. Sagital section demonstrating the prosthesis in position and a hand free tracheostome valve with humidifier. Sudden force of expired air during speech closes the valve automatically. It otherwise remains open during normal breathing.

Supraglottic conservation laryngectomy is a useful procedure for cancer involving the infra-hyoid epiglottis especially with pre-epiglottic space involvement.

Patients may aspirate for a period of time after this operation and therefore selection is important. Results are similar to radiotherapy.

Supracricoid procedures

Supracricoid laryngectomies have proved a significant advance in the management of certain laryngeal and pyriform sinus cancers. Although originally described in 1974 in France (Piquet), they have only recently been popularized in the English-language literature.[20] These procedures preserve the cricoid cartilage and hyoid bone but allow removal of the whole thyroid cartilage in cases of advanced (T4) squamous cell carcinoma of the transglottis. The ability to speak while eating and drinking (no stoma) plays a vital role in French social life. Laccourreye O. et al have also popularized the supracricoid hemi-laryngo-pharyngectomy for early pyriform sinus cancer.[21] This has been a successful procedure at St. Vincent's Hospital, allowing preservation of the larynx, removal of tracheotomy and resumption of swallowing in most patients within three weeks.[22]

THE FUTURE

The weight of evidence for the effect of concomitant chemotherapy and radiotherapy on survival is sufficient to make it a more attractive treatment when compared to radiation alone when radiotherapy is used for curative extent in locally advanced cancer. [23]

Molecular studies on oral cancer (and in laryngeal cancer in unpublished data) at the Garvan Institute have suggested that over expression of Cyclin D1 and under expression of p16 genes predict a poor prognosis.[24]

Laser surgery will play a much greater part in the treatment of primary cancer in the future because of its cost effectiveness as one stage treatment and its low morbidity in reducing the bulk of disease before radiotherapy.

REFERENCES

1. The Changing Incidence of Head and Neck Cancers. Larynx: ICD-8 161.Head and Neck Cancer. Edit. Rhys Evans PH, Robin PE and Fielding JWL Castle House.Publications.1983; 2: 20-22.
2. Maier H. et al *Laryngol. Rhinol. Otol.*1991; 70: 93-98)
3. Waterhouse J.et al. Cancer Incidence in Five Continents. Vol.V. IARC Scientific Publications. Lyons. 1989.
4. Stevenson R Scott. Morell Mackenzie. William Heinemann, Medical books Ltd. London. 1946.
5. Cole IE. Unpublished data. Concord Hospital. 1982-91.
6. Glanz H. *Advance in Otolaryngology*.1984; 32: 1-32.
7. Myers MN and Aijaz A. Management of Carcinoma of the Supraglottic Larynx: Current concepts, and future trends. *Laryngoscope* 1996; 106: 559-567.
8. NSW Cancer Council. Survival from Cancer in NSW in 1980-95. www.cancercouncil.com.au/cncinfo/research/reports/survival/guide.htm
9. Ho Chui M et al. Submucosal tumour extension in Hypo-pharyngeal Cancer. Arch. *Otolaryngol/ Head and Neck Surg* 1997; 123: 964.
10. Theile DR, Robinson DW, Theile DE, Coman WB. Free jejunal interposition reconstruction after pharyngolaryngectomy: 201 consecutive cases. *Head and Neck* 1995;17:83-88.
11. Singer MI and Blom ED. An endoscopic technique for restoration of voice after Laryngectomy. Ann.Otol.1980;89: 529-533.
12. Panje WR. Prosthetic voice rehabilitation following laryngectomy: The voice button. *Ann.Otol.*1981;90: 116-121.
13. Cole I and Miller S. Total Laryngectomy with primary voice restoration. *Aust.N.Z.J. Surg.* 1992;62: 279-282.
14. Department of Veteran Affairs Laryngeal Cancer Study. *N Engl.J. Med.*1991; 324: 1685-90.
15. Lefebvre J L et al. Larynx preservation in Pyriform Sinus Cancer: Preliminary Results of a European Organazationn for Research and Treatment of Cancer Phase 111 Trial. *J. Nat. Cancer Institute.*1996:88, No.13: 890-898.
16. Steiner WE. Therapy of Hypo-pharyngeal cancer. part 111: The concept of minimally invasive therapy of cancers of the UADT with special reference to Hypo-pharyngeal cancer and trans-oral laser microsurgery *HNO*. 1995; 43(3):104-112
17. Ambrosch P, Kron M and Steiner W. CO2 laser microsurgery for early Supraglottic carcinoma. *Ann.Otol.Rhinol.Laryngol.*1998:107: 680-688
18. Eckel HE et al. Potential role of trans-oral laser surgery for larynx carcinoma. *Lasers in Surgery and Medecine.*1998; 23; 79-86.
19. Mooney W, Cole IE, Albsoul N and Pearson SA. Salvage Vertical Partial Laryngectomy for radiation failure in early glottic carcinoma. Accepted *ANZJS* 2001.
20. Coman W, Gallagher R et al. Supracricoid laryngectomy: a significant advance in the management of Laryngeal cancer. *Aust.N.Z.J.Surg;*1998; 68:630-634
21. Laccourreye H et al. Supracricoid hemi-laryngo-pharyngectomy. Analysis of 240 cases *Ann.Otol.Rhinol.& Laryngol.* 1987:96:217-221
22. Cole IE, Gallagher R and Bova R. Supracricoid hemi-laryngo-pharyngectomy for early carcinoma of the Pyriform sinus. In publication 2001.
23. Browman GP et al, *Clinical Review Head and Neck.*2001;4:579-589
24. Bova RJ, Quinn DI, Nankervis JS, Cole IE, Sheridan BF, Jensen MJ, Morgan GJ, Hughes CJ and Sutherland RL. Cyclin D1 and p16 expression predict reduced survival in carcinoma of the anterior tongue. *Clinical Cancer Research.*1999; 5: 2810-2819.

The Best Years of Your Life: Reflections on Depression in Young People

The 2001 Sandra David Memorial Lecture

Her Excellency Professor Marie Bashir AC Governor of NSW

The Sandra David commemorative series has addressed a range of challenging areas of science and medicine, medicine and the law, issues of genetics and ethics. It was suggested that my contribution might address an issue of young peoples' mental health which is an area where biological, genetic and psychosocial factors may all be involved in a complex interplay which in adverse circumstances may produce pathological or dysfunctional consequences and, when understood and re-oriented in therapeutic strategies, may influence restoration of function.

In view of the fact that a significant part of my professional life has been spent working as a clinician and then administrator in the domain of mental health, particularly that of children and young people, it is appropriate that I share with you some thoughts on depression in young people across those years of adolescence and young adulthood, so often believed by envious onlookers to be "the best years of your life!"

First, it may be useful to consider the overall context of mental health from a public health perspective.

It is now recognised that the impact of mental illness within the Australian population is becoming a serious and costly public health issue and that, over a lifetime, one in five persons will be affected by a significant mental health problem. Further, in comprehensive, multi-site epidemiological studies in North America (the epidemiological catchment area study), evidence has accumulated that a majority of persons diagnosed with mental health disorders had experienced their initial episode in childhood or adolescence.

Further, a report published in 1996 – "The Global Burden of Disease Study" – a 4-year research collaboration between the World Health Organisation (W.H.O), the World Bank and Harvard School of Public Health, indicated that by the year 2020 depression – depressive disorders – would become the second largest contributor to disease burden in developed countries and the largest contributor in developing countries.

"Burden of Disease", a public health concept, conceptualised by W.H.O., refers to the impact of illness, injury, disability and premature mortality on healthy life. This estimate therefore has implications for health economics, service planning, community and professional education, prevention, early identification and vigilance in identifying co-morbidities (e.g. alcohol and substance abuse). It demands evidence-based management and monitoring of outcomes and response to treatment. Indeed, epidemiological evidence is accumulating worldwide of the considerable dimensions of the problem. The American Association for World Health has estimated that the frequency of people suffering from mental, neurological or addictive disorders was approximately 400 million prior to September 11, 2001.

Epidemiological studies released last year by the Australian Institute of Health and Welfare indicate that the first episode of depression is often experienced in adolescence, a time of significant biological change and diverse psychosocial demands. Further, it can be prone to recurrence.

It is estimated that approximately 24% of young people in Australia will have suffered at least one major depressive episode by the age of 18 years (Australian Institute of Health and Welfare – Australia's Young People – Their health and wellbeing 1999, cat. No. Phe-19, AIHW, Canberra p.87). The study further revealed that "depression is the leading cause of the burden of disease for young Australian women and occurs at three times the rate than that for young men". In a prompt response to this revelation, the NSW Department for Women commissioned a report (published in August 2001) entitled "Young Women's Health; Depression and Risk Taking Behaviour", to analyse this high prevalence of depression among women and girls, the associated risk taking behaviours which impact so substantially on overall health and to seek solutions. (This is an impressive paper, rich in data).

Since depression in the young, particularly young women, frequently co-exists with anxiety, the impact may be considerable, negatively influencing other aspects of the individual's health and wellbeing (including risk for premature sexual activity, teenage pregnancies, alcohol abuse, traffic accidents, drug experimentation, smoking, or eating disorders). It is important to note that substance abuse in young people has often been preceded by significant depression for a number of years and that the addition of drugs and alcohol are likely to perpetuate or even aggravate the depression. This is highly relevant to the work of drug programs and the drug courts.

In regard to unwanted pregnancies, Health Insurance Commission data reveal that in the year 1999-2000 there was approximately 32,289 terminations in N.S.W. In N.S.W. 27% of all pregnancies end in abortion and the proportion for teenagers is 46%.

While depression may occur at three fold the rate in young women as in young men and may contribute substantially to suicidal behaviour, young men may reach a level of depression equally or more severe and, when suicidal ideation or intent follow, completed suicide – usually due to more lethal means in young men – occurs at a much higher rate than with young women. Depression is a major risk factor for suicide and figures for Australia are among the highest in the industrialised world. Over the period 1979-1997 the suicide rate for young Australian males increased by 71% (from 14 to 24 per

100,000). Over the same period the female rate rose from 4.5 to 5.9 per 100,000 which was not regarded as statistically significant.

Whilst there may be other factors implicated in suicide, it is estimated that around 80% of young people who suicide have been suffering from depression and a majority of those have sought help, usually from a General Practitioner in the months prior to their death.

A number of depression awareness and suicide prevention programs have been implemented over recent years, however, and may be starting to make an impact. Preliminary analysis of the 1999 Australian suicide data released a few months ago suggests that, for the first time in 13 years, a trend towards a slight reduction is noted in adolescents and in young adult males.

A major review of the mid 1990's spanning a 10-year period, however, indicated a rising incidence of depression in young people and an earlier age at first onset. Some analysts may argue that these pessimistic developments could be a manifestation of more accurate recognition by practitioners due to a greater understanding of the problem and a more pro-active medical education strategy on the one hand, together with an awareness on the part of family or friends to obtain treatment earlier, with diminishing concern for potential stigma than previously.

Certainly, a fear of stigma bedevils people with mental health problems still and it has been a longstanding factor in those reluctant to seek professional assistance.

A diagnosis of depression as a clinical entity in children and young people had been rejected by a number of eminent and influential international practitioners in the field of child and adolescent psychiatry as recently as the early 1980's due to the considerable influence of the psychoanalytic model. The proponents theorised that a young person would not yet have adequately developed a mature super-ego, that is a well-defined sense of conscience and, by association, an inability to experience shame and guilt. They believed that this was essential in order for depression to develop. This unproven theory failed to acknowledge the biological and psychosocial relationships to depression.

At this stage it is appropriate to clarify the definition of clinical depression as a disorder which can have biological, cognitive and behavioural consequences. This is in contrast to "benign" depression: a normal, transient, unhappy mood which may include despondency, mild to moderate sadness and which may be related to a situation of loss or bereavement with which one can readily identify. Major depressive disorder, the clinical condition, is characterised by a constellation of well defined symptoms present for at least 4-6 weeks.

Considerable scientific evidence now exists that depression in children and young people is characterised by symptom patterns resembling those of adults. These are noted in the operational criteria of the international classification systems (ICD-10 and DSM IV). Feeling consistently miserable or irritable, diminished pleasure or interest in activities previously enjoyed, reduced concentration, appetite or weight change, increased or decreased sleep, diminished energy, feelings of guilt and worthlessness and morbid thoughts of death or dying can usually be elicited in a sensitive assessment.

There may be family concern at deteriorating scholastic performance and conflict over behavioural problems, including experimentation with drugs and alcohol.

However, depressed adolescents tend not to like to talk spontaneously about feelings and may respond angrily to enquiries. Frequently attributed erroneously to adolescent turmoil or "growing pains", the problem may develop unnoticed, lasting up to 9 months or longer. For many the impact of the depressive experience can have serious consequences which include negative effects on family and personal relationships, deteriorating self esteem, serious disruption to education and work prospects, as well as social withdrawal and homelessness. Many studies attest to the fact that there are considerably higher rates of mood disorders and substance abuse amongst homeless youth compared with home based young people.

Whilst research studies may have difficulty methodologically in clarifying whether the state of homelessness pre-dated the development of a major mental health problem, or is the consequence of these problems, community staff working closely with homeless young people strongly support the latter view – that the mental health problems arose first.

Professional colleagues who have provided consultative services over many years to the Mathew Talbot Hostel comment frequently on the significantly much younger age of the homeless men seeking accommodation in recent times.

More severe forms of depressive or affective disorder (known as bipolar or manic depressive disorder and also unipolar disorder) are influenced by genetic predisposition and may have an acute or fulminating presentation in some adolescents. Some episodes may be associated with the psychotic features of hallucinatory phenomena and delusional beliefs. These young people are frequently at risk of the misdiagnosis of schizophrenia and consequently of incomplete treatment.

This severe form of depressive disorder, though uncommon (around 1-3%) in adolescence, requires careful management and meticulous follow up, presenting, as it does, a major upheaval to the important developmental tasks which face adolescents during this critical age period.

For all the reasons presented, in particular the lost years, the wasted potential, the significant risks – many creative programs to meet this challenge have been developed in Australia following an awareness of the dimensions of the problem and the implications of failure to respond.

The National Health & Medical Research Council (N.H.&M.R.C.) established an expert working party that produced a number of strategies to enhance skills in the identification, diagnosis, prevention and management of depression in young people. These included:

- Clinical practice guidelines (a comprehensive reference document) and four supplementary publications.
- Guidelines for general practitioners (a shorter version of the reference document).
- Guidelines for mental health professionals, particularly community based workers.
- A comic book for consumers (Blue Daze), particularly for young people who have limited literacy skills.
- An information booklet, also for consumers which includes a series of short vignettes (multi culturally sensitive) illustrating the varying forms in which depression in young people may present.

General Practitioners who enjoy working with young people (and who do not feel defensive with them) have honed their skills in this area and specially appointed health professionals, under the "School Link" program, have been funded by State health & education to work (after intensive training and continuing supervisory support) within the school environment, identifying and supporting those young people who are at risk.

Can we identify these young people, about to enter "the best years of their lives" – a time of burgeoning intelligence, physical beauty, idealism, altruism, loyalty to friends and dreams of the future – but already at risk?

Proven risk factors include a history of a previous episode of depression, a family history of depression or alcohol abuse, a negative emotional environment (such as persistent parental conflict), examination failure, loss of a job, unemployment and loss of an important relationship.

In Australian Society, certain groups because of traumatic life experiences, often associated with loss, deprivation, poverty and marginalisation are at greater risk. These include young indigenous Australians, young refugees, young homosexual people and young people in custody and those who suffer from chronic physical illness. This depression can be acted out in a range of self-harming ways.

Suicides of indigenous young males exceed all other groups and have occurred as young as 8 years of age. Reported cases have described determined efforts such as climbing electricity poles to grasp the live wires. Clinics at the Aboriginal Medical Service Redfern, conducted up till a few days before my swearing-in as Governor, regularly included young people from families which had experienced removal, and where family members had gone on to experience loss after loss including sexual abuse in their placements away from home in the aftermath of their removal.

On the other hand, research studies have also identified the presence of protective factors which reduce the likelihood of depression, such as having a good relationship with a parent, good peer attachments and having employment.

Pathways of treatment at an individual level in this age group are enhanced within the framework of a trusting therapeutic alliance – often fragile – always necessary.

It is noteworthy that despite the abundance of anti-depressant medications, and the oft acclaimed greater efficacy of new age medications, successful response in the more common type of depression is limited in this age group, apart from a subgroup in whom anxiety and irritability are prominent features.

Of significant importance are counselling approaches which include educating young people to understand and to manage better the depressogenic factors which may be influential in their life, working with the family and, if required, with the appropriate person in the school.

Issues of confidentiality and sensitivity are paramount. On occasions the counsellor, or general practitioner or adolescent physician involved may find themselves in the privileged role of advocate.

It is essential also to consider the public health/population health context which was introduced at the beginning of this presentation.

Support is required across the whole population for families identified at risk and for vulnerable children beginning even in the antenatal period, early childhood and primary school years. These recommendations are based on the positive evidence of longitudinal studies – involving good early intervention programs.

Most inspiring is that this model is building bridges across the intersectoral boundaries of government departments, non-government organisations, churches and volunteers, creating genuine partnerships and the beginning of renewed social capital.

And what of the wider environment and its capacity for toxic influence?

During the years of the Cold War, young people around the world frequently expressed fears of a nuclear holocaust and the reckless disregard for human life which they perceived from international leaders. In the years of adolescent idealism, contemporary social factors still concern them.

I am now privileged as Governor to meet regularly at Government House with hundreds of year 11 and year 12 young people from across the state. These are very impressive young people from public and private schools. Invariably they raise issues of reconciliation, of threats to the environment, of adolescent depression and suicide. Some speak of a need for spiritual renewal in order to make a contribution to their lives.

It has been pointed out that the rise in depression in adolescents, and I quote, "has occurred in developed countries at a time of political stability, in communities by and large untouched by war and with social welfare systems". Theorists, including the celebrated Durkheim, have postulated that during such periods, anomic influences and a reduction in social cohesion may prevail.

Other explanations have been sought in an examination of contemporary societal values and the tendency to focus on the rights and wellbeing of self with less concern for others, in an environment which promotes material gratification.

Whatever the complex contributory factors, solutions must be sought – and hopefully – found. This is a challenge for the whole of our society.

REFERENCES

1. Robins LN, Reger DA eds. Psychiatric Disorders In America: *The Epidemiologic Catchment Area Study New York*; Free Press 1991.
2. Murray JL & Lopez AD. *The Global Burden Of Disease; A Comprehensive Assessment Of Mortality And Disability From Diseases, Injuries And Risk Factors In 1990 And Projected To 2020* Harvard School Of Public Health, W.H.O. 1996
3. Australian Institute of Health and Welfare – *Australia's Young People – Their Health And Wellbeing 1999* Cat. No. PHE-19 AIHW, Canberra P.87
4. *Young Women's Health: Depression And Risk Taking Behaviour*. N.S.W. Dept. For Women Report August 2001
5. *Young Women's Health: Depression And Risk Taking Behaviour*. N.S.W. Dept. For Women Report August 2001
6. *'Suicides In Australia'* Cat. 3309 1921-1998: Australian Bureau of Statistics
7. Birmaher B, Rayn D, Williamson DE, Brent DA, Kaufman J, Dahl RE, et al. *Childhood and adolescent depression, a review of the past 10 years part 1*. Journal of the American Academy Of Child And Adolescent Psychiatry 1996: 35: 1427 – 1439
8. Parker G & Roy K. *Adolescent depression: a review*. Australian & New Zealand Journal Of Psychiatry 2001; 35:572-580.
9. Robins LN, Reger DA, eds. *Psychiatric disorders in America: the epidemiologic catchment area study New York* ; Free Press, 1991.
10. Kamieniecki GW. *Relevance of psychological distress and psychiatric disorders among homeless young in Australia: a comparative review* Australia & New Zealand Journal Of Psychiatry 2001: 35; 352-258.
11. National Health & Medical Research Council (N.H.&M.R.C.) Publication CP38 *Clinical Practice Guidelines On Depression Young People"*
12. Parker G, Roy K. *Adolescent depression: a review*. Australian & New Zealand Journal of Psychiatry 2001; 35:572-580.

ST VINCENT'S CLINIC FOUNDATION
RESEARCH GRANTS 2002

SISTER MARY BERNICE RESEARCH AWARD 1 - FUNDED BY ST VINCENT'S PRIVATE HOSPITAL AND CLINIC LADIES' COMMITTEE - $100 000.00

A/Professor Robyn Ward

"Identification of a new hereditary colorectal and breast cancer syndrome – the methylator phenotype"

K & A COLLINS AWARD - $50 000.00

Dr Alan Meagher

"Serrated Polyps – Defining their role in the development of colorectal cancer"

SR. MARY BERNICE AWARD 2 – FUNDED BY ST VINCENT'S PRIVATE HOSPITAL AND CLINIC LADIES' COMMITTEE – $25 000.00

Dr Helen Tao

"Multilineage potential of human bone marrow cells"

DI BOYD CANCER RESEARCH AWARD – $20 000.00

Dr Robyn Lukeis

"Whole genomic DNA analysis of colorectal tumours – detection of whole genomic gains and losses by comparative genomic hybridisation (CGH)"

ANNUAL RESEARCH AWARDS – $20 000.00 EACH

Dr L Girgis

"Gene expression in mechanically loaded human oesteoarthritic chondrocytes"

Dr J Low

The value of combining sensitive d-dimer assay and clinical score as a negative predictor in the diagnosis of deep venous thrombosis (DVT)

Dr A Biankin

Novel gene discovery in the development and progression of pancreatic cancer

Prof RSA Lord

Investigation of structural and functional characteristics of vascular dendritic cells in situ and in vitro

Dr D Fatkin

Molecular pathogenesis in dilated cardiomyopathy

ADDITIONAL AWARD – $15 000.00

Dr Vince Lamaro

"Effect of inanimate laproscopic training laboratory on patient management and staff training"