Brachytherapy – One Man's Meat, A Personal Journey in Radiation Oncology

TH Khor,[1,2] *DMRT, FRCR, FAMS*

Abstract

The Lecture covers the author's personal experience in brachytherapy in radiation oncology, beginning with low-dose rate (LDR) treatments using ^{226}Ra "hot" sources, in the 1960s and early 1970s, through manual afterloading for treating gynaecological cancers with the same sources in the 1970s and 1980s, to high-dose rate (HDR) remote afterloading on a microSelectron HDR machine, from 1989 on. This progression in brachytherapy is discussed, and specific applications to various tumour sites are presented, including long-term results of a personal series of 106 patients with cancer of the uterine cervix, treated with radiotherapy incorporating HDR brachytherapy. The Lecture rounds off with an unusual case of equine sarcoid, treated with a postoperative implant, using ^{192}Ir LDR brachytherapy.

Ann Acad Med Singapore 2005;34:399-404

Key words: Equine sarcoid, High-dose rate brachytherapy, Low-dose rate brachytherapy, Radiotherapy, Uterine cervix cancer

Dr Tan Kim Ping, Chairman for the Dr FY Khoo Memorial Lecture, Ladies and Gentlemen – It is a signal honour for me to deliver this Lecture, the second since the Inaugural Lecture last year. Sadly, it has been renamed a Memorial Lecture, as Dr FY Khoo passed away a few months ago, towards the end of 2004. By right, the honour should go to Dr Tan Ban Cheng, who is the most senior Radiation Oncologist in Singapore. However, he had to decline the invitation on grounds of poor health, and I am in a sense giving this Lecture on his behalf. I am also grateful to Dr Chua Eu Jin for his very kind remarks in the citation he read preceding the Lecture.

Building on the Past

I was posted to Radiotherapy, Singapore General Hospital in March 1967, when it was still a division of Radiology, with Dr FY Khoo as the Head of Department. The radiotherapists, as they were then called, were Dr Chia Kim Boon, head of the Radiotherapy Section, Dr Tan Yoke Kwang and Dr Tan Ban Cheng. It was my first posting as a Medical Officer, both unexpected and somewhat unwelcome! I had seen the Medical Superintendent of the Singapore General Hospital, on learning of the posting, to voice my concern. He assured me that he would post me out after 6 months, should I not wish to train in Radiotherapy. The 6 months passed into years and then decades. Dr Chua mentioned my stint in Surgical "B" Unit under the redoubtable Mr Yahya Cohen. At that time, Mr Cohen insisted that any new cancer patient in his department was to be seen by a radiotherapist as a part of the management. Naturally, as the "new kid on the block", I saw quite a few of these patients, either in the wards or at the Radiotherapy Clinic. On learning that I was training in Medical Radiotherapy, without a posting in Surgery (apparently Orthopaedics did not count!), he arranged to correct this deficiency. This surgical exposure certainly contributed to the interest I was to develop in brachytherapy, and I owe a debt of gratitude to Mr Cohen, and even more to the Radiotherapists named, who were the pioneers of the specialty in Singapore.

Brachytherapy

Brachytherapy is short distance treatment, typically 5 mm to 20 mm, and usually with a sealed radioactive isotope as the source of ionising radiation. It was the first application of radiation treatment for cancer, after the Curies (Marie and Pierre) discovered radium in the late 19th century. Teletherapy, in contrast, is long distance

[1] Consultant Radiation Oncologist
Mount Elizabeth Oncology Centre, Singapore
[2] Visiting Consultant, Radiation Oncology
National Cancer Centre, Singapore
Address for Reprints: Dr Khor Tong Hong, Mount Elizabeth Oncology Centre, 3 Mount Elizabeth, Singapore 228510.

treatment, typically from 50 cm to 100 cm. The dose distribution characteristics between the 2 modalities are quite different, with less homogeneity and lower percentage depth dose for brachytherapy, making it a much better choice for treating small, accessible tumours without nodal metastasis. These differences derive mainly from the operation of the Inverse Square Law when photons are being used in brachy- or tele-therapy. For more locally extensive cancers, brachytherapy could still be used, but in combination with teletherapy, combining the dose distribution characteristics of the 2 modes for optimum radiation therapy. Brachytherapy has been termed the "poor man's IMRT (intensity modulated radiation therapy)". Dr Dan Ash, an acknowledged expert on brachytherapy, refers to it as "the original MRT", in his Keynote Address to be delivered at the upcoming Royal College of Radiologists meeting in the UK.

Progression of Brachytherapy in Singapore

We were using ^{226}Ra "hot sources" for brachytherapy up till late 1968, when manual afterloading was introduced for treating uterine cervix cancer, using Fletcher-Suit applicators. The treatment was performed in this hospital, then known as the Kandang Kerbau Maternity Hospital, not far from the auditorium we are in presently. Radium needles continued to be used for interstitial implants at the Singapore General Hospital until the 1990s.

Insertion of the "hot sources", comprising an intrauterine tandem and a pair of ovoids, which were separated by a loose spacer, called for considerable dexterity. The full complement of sources had to be available, behind thick lead slabs to shield staff in the operating theatre from undue exposure. The patients were then transferred 1 floor down to have check X-ray films made, before being sent 2 floors up to the isolation room if the check proved satisfactory. All staff handling these patients post-insertion would have received some radiation dose. More seriously, for the patients, there was no way of determining any displacement of the sources during treatment, which lasted 72 hours. Such displacement would produce a lower dose at the tumour and a higher dose to the rectum – truly a double jeopardy of both poorer tumour control and higher morbidity.

Manual afterloading was a vast improvement, both for staff protection, and for tumour control/treatment morbidity. Radiation exposure was now limited to the radiotherapist loading or unloading the applicators, and to the attending nursing staff. I remember well carrying the radium to and from the radium "safe" located in the operating theatre and the isolation room, at a brisk pace. One had a choice of using a lead pot to shield the radium sources, or of using a large kidney dish held at arm's length, to transport the radioactive sources; I chose the latter mode. Other staff would keep a respectful distance from one during this "radium run"!

The specific activity of radium resulted in low-dose rate (LDR) treatments. With the protection and safety problems associated with radium, other radioactive isotopes were introduced, including ^{137}Cs, ^{192}Ir and ^{60}Co. These isotopes are produced in nuclear reactors and have specific activities much higher than ^{226}Ra, leading to intermediate-dose and high-dose rate (HDR) treatments becoming available.

When I left the Singapore General Hospital in 1989 to start radiotherapy at Mount Elizabeth Hospital, a microSelectron HDR machine had been ordered by the administration. This uses a single high-activity ^{192}Ir source driven by a very precise stepper motor, to deliver remote afterloading HDR brachytherapy. The source would now be transferred in and out of the applicators by the computer controlled stepper motor, a much more elegant mode of transport than my previous practice of holding a kidney dish of radium tubes at arm's length!

HDR remote afterloading with this very small iridium source offered the following benefits: (a) increased accuracy of treatment, (b) protection of personnel from radiation, (c) patient preference for outpatient treatment, and (d) new applications, eg, for cancers of the bronchus and the biliary ducts. However, HDR carries the disadvantages of a high initial and maintenance cost, and an inferior radiobiological effect on the tumour/normal tissue. In theory, an HDR treatment dose could be chosen to match LDR therapy for the same tumour effect, but with higher side effects for normal tissue. Alternatively, a dose could be given to have similar normal tissue effect at the expense of poorer tumour control. However, this theoretical disadvantage has not been seen in clinical practice.

This novel technique, especially using HDR treatment, together with the radiotherapy facility being the first in private practice in Singapore, convinced the Hospital Administration to send me to the UK and the West Coast of the USA to familiarise myself with the HDR machine in clinical use. Much valuable expertise was gleaned from the following specialists:- Dr Peter Blake at the Royal Marsden Hospital, London, UK and Dr Robert Kagan at the Southern California Kaiser Permanente Hospital, Los Angeles, USA in treating gynaecological malignancies, and from Dr Stout at the Christie Hospital, Manchester, UK in endobronchial and intraoesophageal HDR brachytherapy.

Personal Experience at Mount Elizabeth Hospital

Bronchus

A case is shown to illustrate the use of endobronchial brachytherapy in treating an endobronchial tumour in the right intermediate bronchus, which caused haemoptysis and atelectasis. The treatment was combined with external teletherapy, as there was significant extrabronchial tumour mass on CT imaging. The patient had received similar combined external therapy and endobronchial treatment 2 years before.

Gastrointestinal Tract: The Oesophagus

Combined external radiation and intraluminal brachytherapy in a 74-year-old male with squamous carcinoma of the middle third oesophagus. The patient is still alive and well 14 years later. However, this is the exception rather than the rule for oesophageal cancers, and few patients have long-term tumour control, even when treated to radical doses.

Gastrointestinal Tract – The Common Bile Duct

Treatment is palliative and the case shown was for tumour obstruction of the common bile duct. Access to the obstructed duct was via a percutaneous transhepatic cannula, and brachytherapy was delivered after external radiation, in 2 treatments.

Gastrointestinal Tract – The Rectum

The patient had an unusual recurrence of a previous sigmoid colon cancer, involving the left rectal wall and perirectal tissues, probably from transcoelomic spread. There was no evidence of tumour activity at other sites, on positron emission tomography-CT scanning. An interstitial implant was placed when the residual mass was resected after chemoradiation to reduce the tumour bulk. Fractionated brachytherapy was delivered via the implanted polyamide tubes. The patient remains well 16 months after the implant.

Head and Neck – The Nasopharynx

The practice at Mount Elizabeth is to use intracavitary brachytherapy for limited residual or recurrent cancer in the nasopharynx. The tumour depth should not exceed 1 cm on CT imaging and biopsy confirmation is mandatory. Brachytherapy is not given as a boost in primary radiotherapy for nasopharyngeal cancer at our Centre. Four sessions are given, twice a week and 7.5 to 8 Grays (Gy) prescribed at Ho's reference point (1 cm superior to the mid-point between the middle of the "sources" in the right and left applicators), for each treatment.

Head and Neck – The Tongue

Interstitial brachytherapy alone offers comparable cure rates as surgery, for T1/T2N0M0 cancer of the anterior tongue, with the added advantage of tissue preservation. Xerostomia, which would be associated with external beam therapy to a radical dose, is also absent with an interstitial implant, as the sharp fall-off in depth dose "spares" the salivary glands. The orthogonal films shown are for a patient with T1N0M0 squamous cancer of the left lateral, anterior tongue. Fractionated treatment was delivered, to 43 Gy over 5 days in 10 fractions, treating twice daily, with 6 hours between fractions. The dose is prescribed at 0.5 cm from the implant plane.

Head and Neck – The Maxillary Antrum (mould)

A dental mould was made to take 2 polyamide brachytherapy catheters for a boost dose to the upper maxillary antrum and ethmoid sinus. The patient had surgery for recurrent mucoepidermoid cancer of the antrum, with close margins at the superior antrum. Postoperative external beam therapy was given before the brachytherapy boost. The patient remained disease-free for over 7 years until she was lost to follow-up.

Head and Neck – The Tonsil with Neck Lymph Nodes

This 54-year-old Chinese male had a right tonsil cancer with metastatic neck nodes on the same side, diagnosed 4 months after completing adjuvant radiotherapy (60 Gy in 6 weeks) to the right neck for squamous cancer in the cervical nodes. The right neck nodes had been resected, together with the ipsilateral parotid and submandibular salivary glands, following which he was given chemotherapy. The presumed diagnosis then was a salivary gland primary. He had a radical resection of the tonsil primary with radical neck dissection and a myocutaneous flap. Eight polyamide catheters were implanted at surgery and brachytherapy given, as no further definitive external radiotherapy could be offered. The implant was treated to 33 Gy in 10 fractions, over 5 days with 2 fractions per day.

Head and Neck – Pterygium

This is an extreme example of short-distance therapy, being contact treatment using beta irradiation. The eye plaque is coated with ^{90}Sr and applied to the conjunctiva, delivering a single, surface dose of 22 Gy. Therapy is given after excision of the pterygium, either on the same day as surgery or on the following day, to reduce the recurrence risk from almost 30% to about 2%.

Gynaecology – The Uterine Cervix

<u>Radical Radiotherapy Incorporating HDR Brachytherapy – Long-term Results</u>

<u>Introduction</u>: The results of radical radiotherapy for 106 patients with invasive cancer of the uterine cervix are presented. The patients were treated from January 1990 to December 1993, with external pelvic radiotherapy, using 6MV photons and HDR brachytherapy on the micro-Selectron HDR machine. Data analysis was undertaken in November 2004, with the assistance of Dr Ivan Tham and Dr Jeffrey Tuan of Therapeutic Radiology, National Cancer Centre.

<u>Age</u>: The age range was 32-80 years, with a median of 57 years.

Histology: 92.4% had squamous cell carcinoma, 6.6% had adenocarcinoma and 0.9% were reported to have adenosquamous cancer.

Stage at presentation: The distribution by stage is shown in Table 1. More than half of the patients (60.4%) presented with Stages IB and II disease, with most of the remainder having Stage IIIB tumour. Only 4 patients (3.8%) presented with Stage IVA disease, all with invasion of the bladder base.

External pelvic radiotherapy: Pelvic radiotherapy was delivered with 6MV photons, with AP-PA ports up to the third quarter of 1990 (16 patients), after which treatment was given on a four-port, box technique. Daily fractions of 1.8 Gy were used, to 45 Gy for early-stage disease and 50.4 Gy for more extensive tumours. A few patients received parametrial boost treatments, to a maximum of 64.8 Gy. Treatment was delivered daily, 5 times a week, except on the days they received brachytherapy.

Brachytherapy: Brachytherapy was combined with external pelvic radiation, usually at the third and fourth weeks of treatment for limited bulk disease, for which 3 applications were performed, and towards the end of treatment for the late-stage patients, who received 2 insertions. The majority of insertions were performed with the Royal Marsden Hospital applicator set (Peter Blake), with a few treatments using the MD Anderson Hospital set (Fletcher-Suit-Delclos), when the Delclos mini-ovoids were required to fit the limited vault volumes of these patients. The dose to point "A" ranged from 5 to 7.5 Gy for each insertion, with a mean total dose of 17.17 Gy and a median of 18 Gy.

Survival: The overall survival results according to tumour stage are shown in Figures 1 and 2, with a breakdown of Stage IB patients in Figure 3, which show that the 3 patients with Stage IB2 disease all did poorly, none surviving the first year. Further analysis showed that all 3 had residual or recurrent tumour within 4 months of completing radiotherapy.

Complications: The complication rates were fairly low, with 2 patients (1.9%) having RTOG grade 2 rectal complaints, 4 patients (3.8%) with grade 2 bladder reactions and vaginal stenosis in 6 cases (5.7%).

Conclusion: HDR brachytherapy is an effective and safe radiation modality, when used with external pelvic therapy, for the long-term control of uterine cervix cancer.

Table 1. Cervix Cancer – Distribution by FIGO Stage

Stage	No. of patients	%
IB1	14	13.2
IB2	3	2.8
IIA/B	47	44.3
IIIB	38	35.8
IVA	4	3.8
All	106	100.0

Gynaecology – The Uterine Corpus

The practice at Mount Elizabeth is to offer vault brachytherapy using a pair of ovoids from the Fletcher-Suit-Delclos set for post-hysterectomy adjuvant therapy, when this is indicated. Two insertions are performed, a week apart, with a dose of 5 Gy prescribed at a vault mucosal depth of 0.5 cm for each treatment. The dose limiting factor would be the rectal dose.

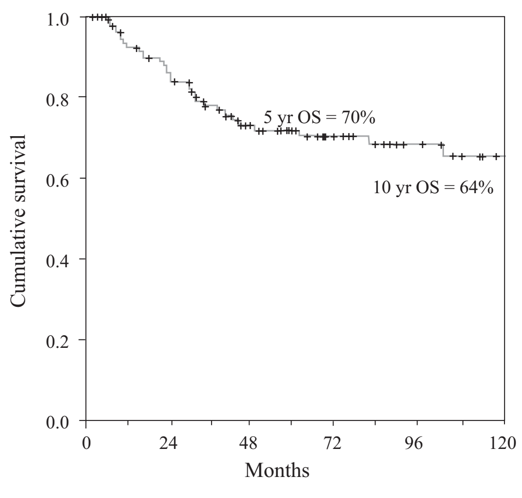

Fig. 1. Overall survival – all stages.

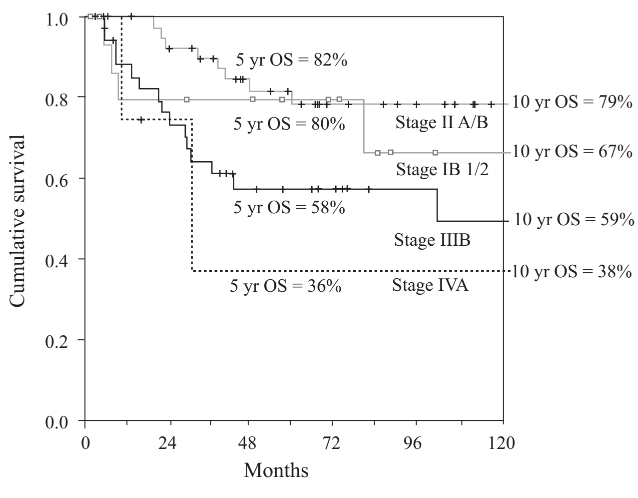

Fig. 2. Overall survival by FIGO stage.

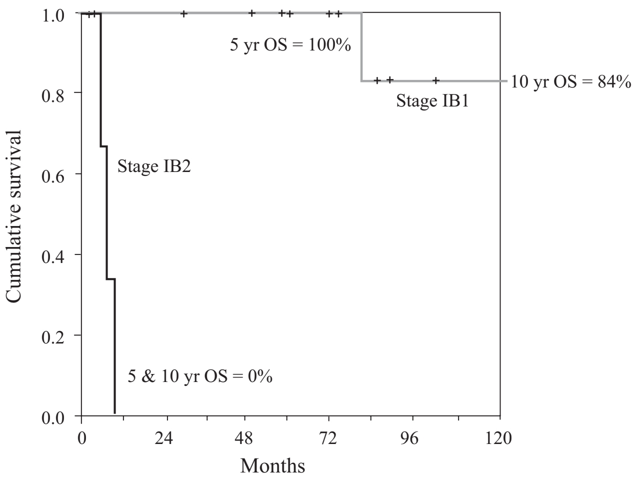

Fig. 3. Overall survival stage IB1 and IB2.

Gynaecology – The Vagina

Vaginal tumours could be irradiated with a cylindrical applicator, provided the tumour is less than 1.0 cm deep. Tumour bulk could be reduced with chemotherapy and external radiotherapy before brachytherapy, as was the treatment for the case shown, of an unusual metastasis to the lower vagina from renal cell cancer. The rectal dose is again the limiting factor, and a fraction size of 5 Gy at 0.5 cm depth, for up to 3 fractions at HDR, combined with 45 Gy external therapy, is generally considered within rectal tolerance.

The Breast – MammoSite Implant

The MammoSite implant was cleared by the US Food and Drug Administration in May 2002, for brachytherapy when the physician chooses to deliver intracavitary radiation to the surgical margins following lumpectomy for breast cancer. This offers suitable patients the convenience of completing adjuvant radiation within a week, compared to the 5 to 6 weeks with whole breast irradiation. The selection criteria include patients' age (45 years and above) and tumour characteristics (unifocal tumour of up to 3-cm maximum diameter, invasive ductal or ductal in-situ cancer). The balloon catheter is implanted into the lumpectomy cavity and the balloon inflated to fill the cavity. Treatment is given to a "rind" of tissue around the cavity wall, of 1-cm thickness. Ten fractions of 3.4 Gy are delivered to the surface of this 1-cm "rind", treating twice a day, with an inter-fraction time of 6 hours. The treatment of the first patient at Mount Elizabeth Hospital is presented.

The Brain – Glioblastoma Multiforme

HDR brachytherapy boost was given to a patient with glioblastoma of her frontal lobes, following surgery and external beam radiotherapy. The catheters were implanted under stereotactic guidance by the neurosurgeon at Tan Tock Seng Hospital. The implant comprise a central catheter and 6 circumferential catheters, at a radius of 2 cm, to encompass the residual tumour mass. The treatment was performed in 1993, and brain implants have largely been replaced by stereotactic external beam therapy, as this modality has become more readily available.

A Horse Tale – Needle (Iridium Wire) in a Haystack

This was my sole attempt at veterinary radiotherapy, and began with a telephone enquiry from a Singapore Turf Club veterinarian. He asked whether I was prepared to implant a racehorse with equine sarcoid involving the left upper eyelid, extending into the lower lid. He had no personal experience of such treatment, but referred me to a Dr Knottenbelt in Liverpool, England, who was an expert in the management of this tumour. Dr Knottenbelt and I entered into an email correspondence, culminating in a telephone conversation, from which I learnt that equine sarcoid is a low-grade fibrosarcoma, which rarely metastasises, but recurs often after surgical resection. He assured me that LDR iridium implant at resection is the treatment of choice, and that a relatively high dose of 90 to 100 Gy would be needed to prevent tumour recurrence. Horses have a much higher tissue tolerance to radiation than humans, he informed me cheerfully!

Clearance was obtained from the relevant authorities to carry out the implant at the Animal Hospital, Singapore Turf Club and the procedure was performed immediately following surgery, using 7 parallel catheters, loaded with ^{192}Ir wire for LDR brachytherapy. Mr Toh, our physicist and I were assured that a collar would be attached, so the horse would not rub the implanted eyelids and dislodge the catheters during the 7 days of the treatment, with the animal in an isolation stall. Daily digital photographs of the implanted area would be sent by email to us.

All went well until the fourth postoperative day, when the veterinary surgeon called to inform us that 1 catheter was missing, with an email photograph confirming this unwelcome news. The promised collar had not been used, because it was too loose for the "patient"! We left for the Turf Club post haste, armed with a Geiger-Muller counter, after leaving strict instructions that nothing was to be removed from the isolation stall. A radiation survey of the stall did not show any "hot" area; running the counter over the horse's flanks also drew a blank. We therefore presumed that the wire in the catheter had come loose, fallen into the hay and been ingested by the horse. The radioactivity was probably too low to be detected by the instrument, through the thickness of absorbing tissues between the gastrointestinal tract and the skin. The Geiger counter was left with the stable staff, who were instructed to monitor the hay that was swept out daily, before it was disposed of. They reported no radioactivity over the background each day. On the final treatment day, Mr Toh and I went to the Animal Hospital, where I removed the 6 catheters with the enclosed iridium wires from the horse. The stable staff told us the hay for disposal had been monitored and had not shown any increased radioactivity.

Fortunately, Mr Toh did a “sweep” of the stall and surroundings himself and detected an increased reading from the hay in the bin outside the stall, due for disposal within an hour! The “needle” was finally located in the “haystack” at the very last minute. We all heaved a sigh of relief, as the consequence of not retrieving the missing wire would have jeopardised our good standing with the Radiation Protection Inspectorate (now known as the Centre for Radiation Protection). The horse is doing well, and was still racing when I last enquired.

Concluding Remarks

With the conclusion of this horse tale, I end my tale and thank you for your kind attention, trusting that the Lecture has succeeded in rekindling some interest in brachytherapy amongst the oncologists present.

Acknowledgements

I am glad to acknowledge the invaluable assistance of Mr Toh Hong Jin, Physicist, Mount Elizabeth Oncology Centre, in planning the brachytherapy treatments on which the Lecture is based, and that of Mdm Ho Mei Ngoh, Chief Radiographer and her dedicated team for delivering the treatments. My thanks also to Dr Ivan Tham and Dr Jeffrey Tuan for their help in data analysis of the uterine cervix series, and to Dr Vijay K Sethi, Head of Radiation Oncology, National Cancer Centre, for assigning them to the project.