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Review

Modern Brachytherapy: Current State and Future Prospects

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This article reviews the current trends and future developments in brachytherapy. Established techniques including interstitial and high-dose rate brachytherapy are discussed with particular reference to lung, oesophageal, cervical and endometrial cancer. Intra-operative high-dose rate brachytherapy and other new tehniques are also mentioned. © **1997 Published by Elsevier Science Ltd**

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INTRODUCTION AND HISTORICAL BACKGROUND

EXTERNAL BEAM (EBR) and brachytherapy (BRT) (from the Greek meaning at a short distance) are the two principle types of radiotherapy. This article reviews the current trends and future developments in BRT. It is a highly selective means of delivering radiation by insertion of radioactive sources directly into tumours. There are two main forms of BRT: interstitial therapy where the sources are implanted directly into the tumour (for example, a cancer of the base of the tongue) (Figure 1) and intracavitary therapy where the sources are inserted into a natural body cavity, for example, the uterus.

It can be used alone or in combination with EBR to boost medium- or small-sized target volumes. BRT often allows higher doses (70–90 Gy) to be delivered to the target volume compared with conventional EBR (60–70 Gy). This is due to a rapid fall off in dose with increasing distance from the source. In contrast, the inclusion of larger volumes with EBR compared with BRT often limits the dose of EBR that can be given within normal tissues. As a result, very high local control rates can be obtained, e.g. in small primary tumours of the cervix and head and neck cancers.

Radium (^{226}Ra) has been in use from the beginning of this century up to the 1960s and even 1970s in many countries. However, in the 1950s with the development of high-energy linear accelerators able to deliver safely high doses to deep-seated tumours, the use of BRT declined. There were three main reasons. First, the fixed shape of the sources limited their adaptability in treating different tumour volumes. Second, high-energy beams required heavy and expensive lead shielding. Third, there was unacceptable radiation exposure to medical and nursing staff. Furthermore, as one of the decay products of ^{226}Ra was a radioactive gas, radon (^{222}Rn), frequent checks on the quality of the sealed sources were mandatory. Finally, the long period of decay of ^{226}Ra (1620 years) might be considered as a major environmental hazard, especially in case of source leakage, breakage or loss.

The last 20 years has seen an expansion in the use of BRT particularly of solid-state caesium (^{137}Cs) and iridium (^{192}Ir). For instance, a typical ^{192}Ir source for high-dose rate afterloading contains 10 Curies in a capsule 2–4 mm long and less than 1 mm in diameter, replacing the old and heavy equivalent 10 mg ^{226}Ra sources. Indeed, the miniaturisation of sources is one of the major advances in BRT and the basis of modern afterloading techniques, especially in interstitial BRT.

Principles of afterloading

Having defined precisely the target volume, the brachytherapist implants the vectors for the sources. These vectors may be hollow plastic tubes or rigid needles. The target volume is defined by clinical observation and radiological findings based on pre- or intra-operative imaging techniques e.g. echography, CT scan, MRI, and moreover by surgical findings (inspection, palpation, frozen sections) which provide important additional information. The next step is insertion of the radioactive sources into the vectors. This two-step procedure significantly reduces the radiation exposure to staff.

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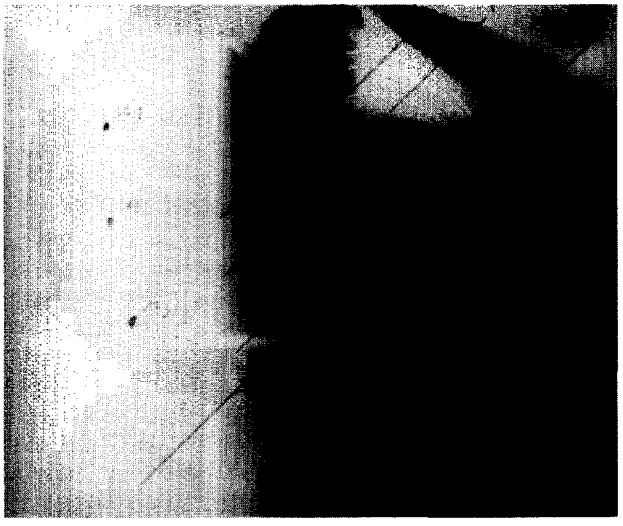


Figure 1. Brachytherapy of the oropharynx. After 60 Gy EBR, a BRT boost has delivered 25 Gy in the base of the tongue. ^{192}Ir wires are located before and behind the hoïd bone.

Alternatives to afterloading: the permanent implants

In situations where the insertion of vectors is difficult (deep-seated tumours, uneven surfaces) or less comfortable for the patient, radioactive sources with particularly low-energy beams, such as iodine (^{125}I), can be implanted definitely and safely into the target volume.

Organ motion

With EBR, organ movement, e.g. lung, prostate, bladder, tongue, may interfere with the daily reproducibility of radiation fields. This problem is overcome by interstitial implantation of sources which are moving with the organ implanted.

Dose rate

BRT technologies can deliver radiation at different dose rates. These are classified as (1) low-dose rate (LDR) (0.4–2 Gy per h), (2) medium-dose rate (MDR) (> 2–12 Gy per h) and (3) high-dose rate (> 12 Gy per h). LDR has remained the safest dose rate, with respect to the tolerance of critical organs. The very low-dose rates (< 0.4 Gy/h) allow re-irradiation of tissues, with the lowest risks of late side-effects. MDR and HDR have the advantage of shortening overall treatment times.

ESTABLISHED TECHNIQUES IN BRACHYTHERAPY

^{192}Ir and ^{137}Cs are the main isotopes used in afterloaded LDR or MDR. Different systems of irradiation and dosimetry are used internationally—the Paris and Manchester systems are mainly used in Europe and the Quimby systems in the United States. Patients are confined to shielded rooms in hospital for 4–8 days depending on the total dose and dose rate.

Interstitial BRT

Head and neck cancers. Interstitial BRT is a useful conservative and non-mutilating procedure for early stage tumours of the head and neck such as those of the oral cavity [1–3] or oropharynx [4–6] or as a boost after EBR for bulky tumours of the oropharynx [7–10]. BRT allows higher radiation doses (80–90 Gy) to be delivered than is possible with EBR [7–10]. For carcinoma of the base of the tongue, it increases the 5-year local control rates from 65% for EBR alone to 70% for T4 and 87% for T1 tumours. However, the escalation in dose is accompanied by an acceptable 10% rate of transient necrosis of adjacent soft tissue and bone.

Prostate cancers. In stage T2c and T3 prostate cancer, recent techniques combining ^{192}Ir BRT and EBR can deliver 75–85 Gy to the target volume with a high degree of precision. This combination in non-randomised studies increased the local control rate to 89–92% [11–13]. Compared to EBR, ultrasound-guided insertion of the source vectors have improved the accuracy of irradiation and reduced major morbidity (grade III and IV) to < 5% [11–14]. Excluding the problem of prostate motion met with EBR high-precision techniques, it is particularly advantageous in protecting the rectal mucosa from excessive dosage.

Encouraging results have also been recently reported by using permanent ^{125}I and palladium (^{103}Pd) implants in the treatment of early-stage prostate cancer (T1b–T2b). Biochemical control (PSA < 1.0 ng/ml) is obtained in more than 90% of cases [14]. These methods maintain the highest sexual potency rates (> 85%) and do not require more than two days hospitalisation.

BRT combined with surgery or EBR. As a conservative and less mutilating procedure, there is a growing literature on BRT combined with surgery and/or EBR in the treatment of selected sarcomas [15, 16], rectal [17], anal [18], breast [19], bladder [20–22] and advanced cervical cancers [23]. For example, in a recent prospective phase III trial, patients randomised to intra-operative BRT following surgery for undifferentiated sarcomas had a local recurrence rate of 18% compared with 31% after surgery alone ($P = 0.0025$) [16].

For skin cancers of the eyelid, inner canthus, paranasal grooves, external ear, simple BRT techniques offer good cosmesis and can be a good alternative to EBR or to more mutilating or time-consuming surgery [24].

Intracavitary therapy

The principles of intracavitary therapy for cancer of the cervix are well established [25, 26]. Combining EBR and BRT remains the most common treatment for cancer of the cervix [27]. Alternative initial BRT for TIB–TIIb proximal tumours can sterilise microscopic deposits adjacent to the main tumour mass and can be followed by less radical pericervical dissection with lower risks of major complications [26].

Where radiotherapy alone is the primary treatment for cervical or endometrial cancer [25, 27–30], it has been established that BRT combined with EBR doubles the local control rates compared with EBR alone.

LIMITATIONS OF CLASSICAL BRACHYTHERAPY

Lack of randomised trials

While the efficacy of BRT has been demonstrated at many tumour sites, very few randomised trials have been carried out to demonstrate its benefits compared with EBR. The paucity of such trials may be partly explained by the small numbers of patients treated in each individual centre, variation in availability of technical resources in radiotherapy departments and different dosimetric systems hampering international comparison. In addition, the need for inpatient care makes BRT less convenient for patients especially for the increasing population of elderly patients in Western societies.

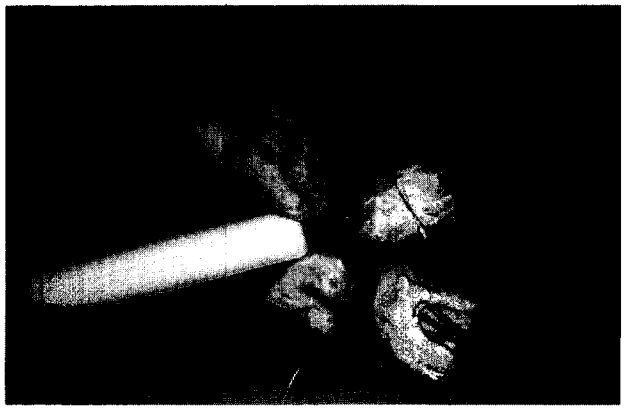
BRT is poorly suited for treating deep-seated tumours (e.g. pancreatic or distal lung tumours), surfaces where tissue contours change rapidly (e.g. neck and pelvic areas) or organs which cannot tolerate intraluminal modern applicators for long periods of time (e.g. bronchus, oesophagus).

Most of the time inpatient BRT remains less cost effective than outpatient EBR. Moreover, when the justified treatment is expected to be successful in a small proportion of the population treated (e.g. using vaginal vault BRT for decreasing local recurrences rates from 15% after surgery alone compared to 3% after combined treatments), the clinical gains have to be balanced against the complications of prolonged hospitalisation, deep venous thrombosis and pulmonary embolism.

NEW DEVELOPMENTS IN BRACHYTHERAPY

High-dose rate BRT

Recently, afterloading systems delivering high-dose rate (HDR) BRT have been developed. A short source (2–4 mm in length) of ^{192}Ir is moved hydraulically in a stepwise manner within the vectors and delivers 2–15 Gy (1–3 Gy/min) per fraction. The treatment is therefore short and can be carried out on an outpatient basis. The HDR unit has often been installed in an existing EBR treatment room and has enabled BRT techniques to be adopted in hospitals which could not afford to build a full shielded ward. In addition, HDR technology has made radiation protection easier and less expensive.



(a)

(b)

Figure 2. The optimisation of vaginal vault BRT with the HDR stepping source technology. (a) Individualised moulds are used to treat different sizes and shapes of the vaginal vault. On the surface of these moulds are inserted the plastic tubes vectors. (b) The reference isodose is represented, passing at a constant distance from the mould surface. Computer optimisation has been used to avoid 'cold or hot spots areas'.

The capacity to vary the position and dwell time of the radiation sources has enabled dose distribution within the tumour volume to be optimised (Figure 2) [31]. The principle disadvantage of HDR BRT is the higher risk of total morbidity. Its therapeutic ratio is lower than for LDR and fractionation of the total dose is often necessary. However, if critical organs can be displaced from the irradiated volume or receive 75–80% or less of the prescribed dose, the problems of the dose rate may be less significant [32–35]. For example, the rectum and bladder can be displaced from the radioactive sources during cervical BRT [32–35].

Current indications for HDR BRT

Lung cancer. This is a very effective means of debulking the endobronchial component of the tumour. In emergency situations, laser therapy followed by BRT offers the security of a rapid and prolonged relief of symptoms [36]. In combination with palliative EBR, symptomatic relief is obtained in the majority of cases (80–90%) with short duration of treatment and low morbidity [37]. Occasionally, BRT appears to be curative for highly selected endobronchial tumours [38]. However, the complication rate (7% fatal haemoptysis and 5% bronchial stenosis) is higher than for EBR.

Oesophageal cancer. In combination with EBR, HDR BRT can increase the total dose delivered [39, 40]. In contrast to HDR, LDR techniques cannot use oesophageal bougies and are unable to maintain the position of the radiation sources in the centre of oesophageal lumen to assure homogeneous irradiation. It has been reported to contribute to the cure of small tumours [39].

Cervical and endometrial cancer. HDR treatment is certainly indicated in old or frail patients for whom classical LDR treatments are medically contra-indicated or refused by the patients. Results from retrospective and randomised studies do not show higher risks of grade III or more late side-effects rates (severe morbidity) [41–43]. A randomised trial has demonstrated that increments of dose rates in the range of the LDR increased grade I and II morbidity [26]. Therefore, even though it is still not definitely known that HDR is equivalent to LDR BRT, there is a growing number of radiation oncologists using HDR.

Intra-operative HDR BRT [44, 45]. After resection of some thoracic, abdominal or pelvic tumours, catheters or customised applicators can be applied to the operative site. Depending on the clinical circumstances, irradiation can be delivered postoperatively by LDR, by HDR in 2 Gy fractions, or intra-operatively in a single fraction if critical organs cannot be excluded from the treatment field after surgery.

New BRT techniques

Ultrasound-guided breast or prostatic implants with direct visualisation of the isodoses on the ultrasound slices has recently been reported [11]. This has the advantage that any adjustment to the geometry of the implant can be carried out intra-operatively to ensure good dose distribution in the target volume.

Many promising isotopes (Table 1) are currently under investigation. ^{103}Pd seeds [46] are similar to ^{125}I but have the advantage of a shorter half-life (17 days) and might therefore be more appropriate for treating tumours with a short doubling time. Moreover, the risk of seed displacement during

Table 1. New radioisotopes used for brachytherapy

	Energy (keV)	Half-life (days)	Half value layer (HVL) in mm of lead	Initial dose rate (cGy/h)	Dose to infinity (Gy)
Iodine-125	27	60	1/40	8	160
Palladium-103	21	17	1/100	20	120
Ytterbium-169	93	32	1/2	13	140

effective irradiation is lower as the treatment time is shorter. Recent data report encouraging results using ^{103}Pd seeds in the treatment of early prostatic cancer [14].

The pulsed dose rate (PDR) afterloading [47, 48] uses the same techniques as HDR afterloading. For the first 10–20 min of every hour, a single source of ^{192}Ir moves into the vector catheters within the tumour delivering a 40–60 cGY pulse. According to Hall and Brenner, the biological efficacy of PDR should equal or even exceed LDR data [47]. However, preliminary experimental and clinical results remain contradictory and results of prospective trials are awaited. Patients have to be confined to shielded rooms for several days as with LDR, although they can be disconnected from the device for the time between pulses. One of the main disadvantages of PDR is the complex radiation protection rules that have to be applied due to the high activity of the ^{192}Ir source (1 Curie) [48].

Finally, plastic catheters have been implanted into the target volume into which hyperthermia probes or radioactive sources are inserted [49, 50]. This therapeutic approach has not been widely tested and remains experimental.

CONCLUSIONS

Brachytherapy is a safe and highly selective radiation technique to be used alone or as a boost to the target volume in combination with EBR. As one third of cancer deaths are still due to local recurrence, the concept of increasing the dose from the commonly delivered 60 Gy to 80 Gy or more is one of the main priorities in radiation treatment research [51, 52]. High (80 Gy or more) total dose can now be delivered with BRT or more recently developed proton or photon conformal therapy. In contrast to proton or conformal therapy, with BRT, the shape and the volume of the implants can be planned not only from imaging data (ultrasonography, CT scans, MRI), but also from surgical findings which provide important additional information.

BRT unlike EBR is not limited by organ movement. However, when treatment is not limited by organ movement (cerebral tumours or choroidal melanomas), non-surgical techniques such as proton therapy or other conformal treatments seem to be more attractive for the patients.

Unlike EBR, BRT can deliver radiation at different dose rates. When critical organs are included in the target volume, low-dose rate BRT is the treatment of choice. High-dose rate BRT is applicable in selected tumours e.g. lung or oesophageal cancers or when critical organs can be displaced from the target volume e.g. cervical cancers.

BRT is cheaper than proton therapy, but in most cases more expensive than conventional EBR. Confining BRT to large centres with significant numbers of patients undergoing BRT improves its cost-effectiveness.

It seems very difficult to initiate the necessary prospective randomised studies to determine the real benefits in comparison with other new selective EBR techniques, e.g. proton and conformal therapy, for two reasons. First, only 10–20% of the patients treated in a department may benefit from BRT. Second, there has been no consensus on an optimum BRT treatment. Finally, even if the importance of brachytherapist's skill declines with the increasing usage of 'on-line' placement of vectors, BRT still requires a high degree of manual dexterity. It should be performed by well-trained physicians in centres accruing large numbers of patients.

1. Mazeron JJ, Grimard L, Raynal M, *et al.* ^{192}Iridium curietherapy for T1 and T2 epidermoid carcinomas of the floor of mouth. *Int J Radiat Oncol Biol Phys* 1990, **18**, 1299–1306.
2. Mazeron JJ, Crook JM, Benck V, *et al.* Iridium 192 implantation of T1, T2 carcinomas of the mobile tongue. *Int J Radiat Oncol Biol Phys* 1990, **19**, 1369–1376.
3. Pernot M, Malissard L, Aletti P, *et al.* Iridium 192 brachytherapy in the management of 147 T2 N0 oral tongue carcinomas treated with irradiation alone: comparison of two treatment techniques. *Radiother Oncol* 1992, **23**, 223–228.
4. Esche BA, Haie CM, Gerbaulet AP, *et al.* Interstitial and external radiotherapy in carcinoma of the soft palate and uvula. *Int J Radiat Oncol Biol Phys* 1988, **15**, 619–625.
5. Mazeron JJ, Lusinchi A, Marinello G, *et al.* Interstitial radiation therapy for squamous cell carcinoma of the tonsillar region: the Creteil experience (1971–1981). *Int J Radiat Oncol Biol Phys* 1986, **12**, 895–900.
6. Son YH, Nori D, Fu KK. *Oropharynx and Hypopharyngeal Lesions. Interstitial Brachytherapy.* New York, Raven Press, 1990, 111–122.
7. Harrison LB, Zelefsky MJ, Armstrong JG, *et al.* Performance status after treatment for squamous cell cancer of the base of tongue. A comparison of primary radiation therapy versus primary surgery. *Int J Radiat Oncol Biol Phys* 1994, **30**, 953–957.
8. Harrison LB, Zelefsky MJ, Sessions RB, *et al.* Base of tongue cancer treated with external beam irradiation plus brachytherapy: oncologic and functional outcome. *Radiology* 1992, **184**, 267–270.
9. Crook J, Mazeron JJ, Marinello G, *et al.* Combined external irradiation and interstitial implantation for T1 and T2 epidermoid carcinomas of base of tongue: the Creteil experience (1971–1981). *Int J Radiat Oncol Biol Phys* 1988, **15**, 105–114.
10. Lusinchi A, Eskandari J, Son Y, *et al.* External irradiation plus curietherapy boost in 108 base of tongue carcinomas. *Int J Radiat Oncol Biol Phys* 1989, **17**, 1191–1197.
11. Martinez A, Stromberg J, Edmundson G, *et al.* On-line conformal HDR dose escalation trial in prostate cancer. *Radiotherapy and Oncology* 1996, **39**(S1), S1.
12. Puthawala A, Syed N, Austin P, *et al.* Combined interstitial Iridium-192 implant and external beam irradiation in the treatment of carcinoma of the prostate. *Radiotherapy and Oncology* 1996, **39**(S1), S1.
13. Kovacs G, Wirth B, Bertermann H, *et al.* Ten years experience in organ preservation using HDR Brachytherapy boost for nodal negative locally advanced prostate cancer. *Radiotherapy and Oncology* 1996, **39**(S1), S1.
14. Porter AT, Blasko JC, Grimm PD, *et al.* Brachytherapy for prostate cancer. *Cancer J Clin* 1995, **45**, 165–178.
15. Habran JL, Gerbaulet A, Pejovic MH, *et al.* Twenty years experience of interstitial iridium brachytherapy in the management of soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 1991, **20**, 405–411.
16. Pisters PT, Harrison LB, Leung DH, *et al.* Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol* 1996, **14**, 859–868.
17. Minsky BD. Conservative management of early rectal cancer. *Int J Radiat Oncol Biol Phys* 1996, **34**, 961–962.
18. Gerard JP, Sentenac I. Anus et Rectum. In Pierquin B, Marinello, GH, eds. *Manuel Pratique de Curiethérapie.* 1992, 209–217.
19. Van Limbergen E. A critical view on brachytherapy in breast cancer. Annual Brachytherapy Meeting, GEC-ESTRO, York, 10–12 May 1995.
20. Hilaris BS, Nori D, Anderson LL. In Hilaris BS, Nori D, Anderson LL, eds. *Brachytherapy in Cancer of the Bladder. Atlas of Brachytherapy.* Macmillan, 1988, 232–242.

21. Rozan R, Albuisson E, Donnarieux D, *et al.* Interstitial Ir192 for bladder cancer (a multicentric survey: 205 patients). *Int J Radiat Oncol Biol Phys* 1992, **24**, 469–477.
22. Van Der Werf-Messing B, Menon RS, Hop WCJ. Cancer of the urinary bladder category T2, T3 (NXM0) treated by interstitial radium implant: second report. *Int J Radiat Oncol Biol Phys* 1983, **9**, 481–485.
23. Martinez A. Interstitial and external beam therapy for the treatment of locally advanced cancers of the female genital tract. Second international brachytherapy and remote afterloading symposium and workshop. Hyatt Regency Hotel, St Louis Union Station, St Louis, Missouri, April 19–21, 1990.
24. Pierquin B, Wilson JF, Chassagne D. In Pierquin B, Wilson JF, Chassagne D, eds. *Skin Brachytherapy. Modern Brachytherapy.* Masson, 1987, 273–285.
25. Pierquin B, Wilson JF, Chassagne D. In Pierquin B, Wilson JF, Chassagne D, eds. *Cervix Brachytherapy. Modern Brachytherapy.* Masson, 1987, 175–203.
26. Lambin P, Gerbaulet A, Kramar A, *et al.* Phase III trial comparing two low dose rates in brachytherapy of cervix carcinoma: report two years. *Int J Radiat Oncol Biol Phys* 1993, **25**, 405–412.
27. Perez CA, Grisby PW, Camel HM, *et al.* Irradiation alone or combined with surgery in Stage IB, IIA, and IIIB carcinoma of uterine cervix: update of a nonrandomized comparison. *Int J Radiat Oncol Biol Phys* 1995, **31**, 703–716.
28. Hilaris BS, Nori D, Anderson LL. In Hilaris BS, Nori D, Anderson LL, eds. *Brachytherapy in Cancer of the Corpus. Atlas of Brachytherapy.* Macmillan, 1988, 258–264.
29. Nori D, Merimsky O, Batata M, *et al.* Postoperative high dose rate intravaginal brachytherapy combined with external irradiation for early stage endometrial cancer: a long-term follow-up. *Int J Radiat Oncol Biol Phys* 1994, **30**, 831–837.
30. Perez CA, Grigsby PW. Irradiation in the management of carcinoma of the endometrium: a review. *Endocurietherapy/Hyperthermia Oncol* 1995, **11**, 67–95.
31. Hoornaert MT, Nickers P, Mitine C, *et al.* The mould applicator in HDR Gynaecological Brachytherapy. Dosimetric and technical aspects. *Radiotherapy and Oncology* 1995, **35**(S1), S7.
32. Brenner DJ, Hall EJ. High dose rate Brachytherapy for carcinoma of the cervix: fractionation considerations. *Int J Radiat Oncol Biol Phys* 1992, **22**, 221–222.
33. Dale RG. The use of small fraction numbers in high dose-rate gynaecological afterloading: some radiobiological considerations. *Br J Radiol* 1990, **63**, 290–294.
34. Stitt JA, Fowler JF, Thomadsen BR, *et al.* High Dose Rate intracavitary brachytherapy for carcinoma of the cervix: the Madison system: I. Clinical and radiobiological considerations. *Int J Radiat Oncol Biol Phys* 1992, **24**, 335–348.
35. Scalliet P, Gerbaulet A, Dubray B. HDR versus LDR gynecological brachytherapy revisited. *Radiotherapy and Oncology* 1993, **28**, 118–126.
36. Bach H, Macha HN, Wahlers B. Palliative endobronchial HDR Brachytherapy in obstructing malignancies: influence on survival and pattern of failure. *Radiotherapy and Oncology* 1996, **39**(S1), S28.
37. Speiser BL, Spartling L. Remote afterloading Brachytherapy for the local control of endobronchial carcinoma. *Int J Radiat Oncol Biol Phys* 1993, **25**, 579–587.
38. Hennequin C, Tredaniel J, Dray M, *et al.* Predictive factors of late toxicity in endobronchial brachytherapy. A multivariate analysis. *Radiotherapy and Oncology* 1995, **35**(S1), S9.
39. Chirat E, Zimmerman P, Marsiglia H, *et al.* Treatment of oesophagus cancer by High Dose Rate brachytherapy. *Radiotherapy and Oncology* 1996, **39**(S1), S43.
40. Hishikawa Y, Taniguchi M, Kamikonya N, *et al.* External beam radiotherapy alone or combined with high-dose rate intracavitary irradiation in the treatment of cancer of the esophagus: autopsy finding in 35 cases. *Radiotherapy and Oncology* 1988, **11**, 223–227.
41. Orton CG, Seyedsadr M, Somnay A. Comparison of high and low dose rate remote afterloading for cervix cancer and the importance of fractionation. *Int J Radiat Oncol Biol Phys* 1991, **21**, 1425–1434.
42. Patel FD, Sharma SC, Negi PS, *et al.* Low dose rate VS High dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: a clinical trial. *Int J Radiat Oncol Biol Phys* 1994, **28**, 335–341.
43. Sarkaria JN, Petereit DG, Stitt JA, *et al.* A comparison of the efficacy and complication rates of low dose-rate versus high dose-rate brachytherapy in the treatment of uterine cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1994, **30**, 75–82.
44. Harrison LB, Mychalczak B, Enker W, *et al.* High dose rate intra-operative radiation therapy for local advanced and recurrent colorectal cancer. *Radiotherapy and Oncology* 1996, **39**(S1), S15.
45. Kolkman IK, Visser AG, Jansen PP, *et al.* Technique for intraoperative HDR Brachytherapy followed by external beam Radiotherapy. *Radiotherapy and Oncology* 1996, **39**(S1), S39.
46. Porrazzo MS, Hilaris BS, Moorthy CR, *et al.* Permanent interstitial implantation using Palladium-103: the New York Medical College preliminary experience. *Int J Radiat Oncol Biol Phys* 1992, **23**, 1033–1036.
47. Brenner DJ, Hall EJ. Conditions for the equivalence of continuous to pulsed low dose rate brachytherapy. *Int J Radiat Oncol Biol Phys* 1991, **20**, 181–190.
48. Hall EJ, Brenner DJ. Pulsed dose rate brachytherapy: can we take advantage of new technology? *Int J Radiat Oncol Biol Phys* 1996, **34**, 511–512.
49. Fu KK, Ling CC, Nath R, *et al. Hyperthermia and Low Dose-Rate Brachytherapy. Insterstitial Brachytherapy.* Interstitial Collaborative Working Group. Raven Press, 1990, 54–55.
50. Hilaris BS, Nori D, Anderson LL. In Hilaris BS, Nori D, Anderson LL. In Hilaris BS, Nori D, Anderson LL, eds. *Hyperthermia and Low Dose-Rate Brachytherapy. Atlas of Brachytherapy.* Macmillan, 1988, 312–321.
51. Suit HD, Westgate SJ. Impact of improved local control on survival. *Int J Radiat Oncol Biol Phys* 1986, **12**, 453–458.
52. Okunieff P, Morgan D, Niemierko A, *et al.* Radiation dose—response of human tumors. *Int J Radiat Oncol Biol Phys* 1995, **32**, 1227–1237.