Chemoradiation - an overview and examples

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Chemoradiation for Carcinoma of the Cervix

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Chemoradiation became the standard treatment for carcinoma of the cervix almost overnight in 1999, replacing radiotherapy. The April 15 1999 issue of The New England Journal of Medicine published three randomised trials of chemoradiation for carcinoma of the cervix. The National Cancer Institute of the United States earlier issued a recommendation that "... strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer". Two more phase III trials were reported later that year, reinforcing the momentum.

Cisplatin, mostly given weekly when added to conventional radiotherapy for the treatment of carcinoma of the cervix, reduced the odds of death ranging from 50% to 28%. The absolute reduction of mortality amounted to 10% to 15%. The practice in Hong Kong followed suit.

A recent Cochrane review (The Cochrane Database of Systematic Reviews 2005 Issue 4) further supports the treatment efficacy of chemoradiation. The database reviewed 24 trials including 4,921 patients. The authors concluded that the evidence "... strongly suggests chemoradiation improves overall survival and progression free survival, whether or not platinum [ie, all we need is chemotherapy] was used, with absolute benefits of 10% and 13%, respectively". They also commented that reports on late toxicities were still lacking. Late radiation toxicity takes years to manifest. The underlying pathology is almost always endarteritis obliterans, stromal atrophy and fibrosis. We are watching cautiously.

Chemoradiation is evolving. Biologics and hypoxic cell killers are now being tested to see if they can be part of the regimen integrated to radiotherapy.

Starting chemoradiation for cancer of the cervix actually gave us an opportunity to familiarise ourselves with this technique. Prior to this, we were trying our hand at advanced head and neck cancers, with the worry that using the two modalities concomitantly might do great harm. The radiotherapy target volume for cancer of the cervix is large, comprising the whole pelvis, including a lot of bowel and bone marrow. Radiation enteritis and bone marrow toxicity were our main concerns; however, these turned out to be manageable. Since then, we have become much more positive and confident in using chemoradiation, extending the application to other cancer sites. The rest is history.

Evolution of Chemoradiation in the Management of Locally Advanced Rectal Cancer in the Post-5-FU Era

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Management of rectal cancer has undergone significant evolution in the last decade. Advances in diagnostic evaluation, meticulous attention to complete excision of mesorectum, judicious use of adjuvant therapy and availability of novel chemotherapeutic agents for patients with advanced disease have culminated in significant improvement in outcomes. In patients with locally advanced rectal cancer, the present standard of care is to offer preoperative fluorouracil (5-FU)-based chemoradiotherapy, which induces downsizing and downstaging that, in turn, facilitates complete resection. Whilst adjuvant chemotherapy with the oxaliplatin-5-FU couplet has become the new standard of care in patients with stage III resected cancer of the colon, the role of novel agents in rectal cancer is still evolving. On a practical level, patients with locally advanced disease harbour significant risks of both local and systemic failures, and in this regard, pre- and postoperative regimens that offer both radiation sensitisation and systemic activity may improve local as well as distant control.

Oxaliplatin is a novel platinum derivative with a 1, 2 diaminocyclohexane (DACH) group. The combination of oxaliplatin and 5-FU has shown superior progression-free survival and 3-year disease-free survival in patients with advanced and stage III colon cancer, respectively. Moreover, oxaliplatin is a potent radiation sensitiser, which renders it an appropriate agent to combine with radiotherapy in rectal cancer. More recently, capecitabine, an oral fluoropyrimidine with selective activation in tumours where there is a relatively high level of thymidine phosphorylase, has been shown to be active in advanced disease, and equivalent to conventional 5-FU plus leucovorin in patients with stage III colon cancer. Moreover, there are data suggesting a synergistic relationship between capecitabine and radiation, a result of the upregulation of thymidine phosphorylase by the latter. The

oxaliplatin and capecitabine couplet has been examined in patients with metastatic colorectal cancer, and preliminary results reveal significant systemic activity in the same order as oxaliplatin plus 5-FU.

Figure 1.3-Dimensional conformal radiotherapy planning in rectal cancer.

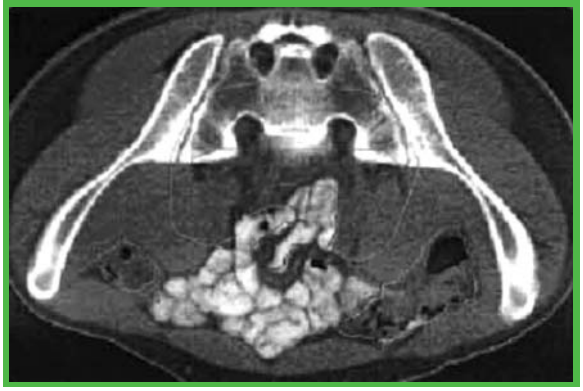
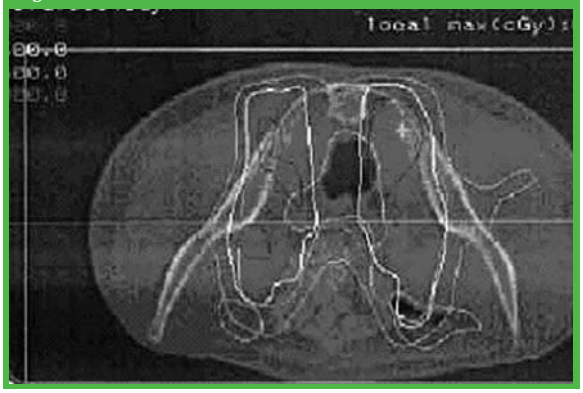


Figure 2. IMRT dose distribution in rectal cancer.



In parallel, there is also momentous innovation in radiotherapy technology, and 3-dimensional radiotherapy planning is increasingly being employed to improve the conformity of radiation dose distribution (Figure 1), a move that has significantly reduced the toxicities over the small bowel and urinary bladder. More advanced conformal techniques, including intensity modulated radiotherapy (IMRT) (Figure 2) and tomotherapy, are also being examined in the field of rectal cancer to further improve the therapeutic ratio.

With such advances in place, are there any clinical data showing benefits of adding oxaliplatin-capecitabine to radiotherapy? There are a number of studies examining the combination of oxaliplatin-capecitabine with radiotherapy in patients with locally advanced rectal cancer and three of these have been published recently. Findings from these studies are summarised in the Table.

An overview of these preliminary data suggests the feasibility and safety of combining radiotherapy with the systemically active oxaliplatin-capecitabine couplet. In addition, the high pathological complete response rates observed across these studies are encouraging, although longer follow-up with specific data on sites of relapses, survival and longterm toxicities are required before it is widely adopted.

In summary, the availability of systemically active agents in the post-5-FU era has shown considerable promise for refining the management of patients with locally advanced rectal cancer, and further data are eagerly awaited.

Table. Recent studies of oxaliplatin-capecitabine with radiotherapy in locally advanced rectal cancer

No. of patients	Patients recruited	Phase of study	Combination studied	pCR rate (%)	RO rate (%)	Significant pathological response (including pCR)	Authors
32	T3-T4 or low-lying rectal cancer	I/II	O: escalating dose between 50mg/m2 and 60mg/m2 weekly C: 825mg/m2 bd on days 1-14 & 22-35 RT: 50.4 Gy	19	79% (T4)	58%	Rodel et al
40 (evaluable:36)	T3-T4 and/or N+	II	O: 50mg/m2 weekly x 5 weeks C: 825mg/m2 bd on each day of RT RT: 45 Gy	14	83% (CRM tumour free)	58% (by Wheeler grade)	Machiels et al
18	Clinically unresectable rectal canceror when histologically clear surgical margins unlikely	I	O: 130mg/m2 on days 1 & 29 C: escalating dose from 500-625-825mg/m2 bd RT: 45 Gy	28	78%	NA	Glynne-Jones et al

O:oxaliplatin; C: capecitabine; RT: radiotherapy; pCR: pathological complete response; RO: complete resection; CRM: drcumferential resection margin; NA: Not available

Chemoradiotherapy of Carcinoma of the Oesophagus

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The incidence of carcinoma of the oesophagus remains high in Hong Kong with a mortality rate of 5 per 100,000 in 2002. It is the 6th most common cause of cancer morality in Hong Kong. The aggressiveness of the disease can be illustrated by the fact that 356 patients died of this disease in 2002, while 472 new cases were diagnosed in the same year. With a recent rise in the incidence of carcinoma at the gastro-oesophageal junction[1], adenocarcinoma has overtaken squamous cell carcinoma as the commonest histology. Because of its location and advanced stage and age at diagnosis (60% of patients diagnosed were older than 65 years), surgical resection can seldom be performed successfully. Even among the selected surgical candidates, the surgical mortality rate is about 5% and the long-term survival is 10% to 40%. There is an obvious need to develop new treatments to improve local control and survival.

Several randomised studies of preoperative chemoradiotherapy have shown impressive results and a resection rate of 70%.[2,3] Clinical complete remission and pathological complete remission rates up to 25% are reported. Definitive chemoradiotherapy is usually used for those advanced disease cases in which surgical resection is not an option.[4] The treatment result in these patients is expected to be poor because the metastatic rate is high. A randomised study using cisplatinium and 5-fluorouracil (5-FU) plus concurrent radiotherapy has shown a 5-year survival rate of 32% and 10-year survival rate of 20%.[5] The relatively low dose of radiation used (50 Gy) and the good local control of disease in the study have demonstrated the synergistic effect of combined chemotherapy and radiation.

Case 1. A 62-year-old male smoker presented in July 2000 with dysphagia and weight loss of 10 kg. He underwent a barium swallow test and CT scan (Figure 1a), which revealed an occlusive lesion at the mid-oesophagus level. Oesophagastroduodenoscopy (OGD) was performed with biopsy confirming a moderately differentiated carcinoma extending from 22 to 26 cm.
The patient received radical chemoradiation with two cycles of IV cisplatinium 100 mg/m^2 on day 1 and 5-FU 1,000 mg/m^2 on day 1 to day 4 every 3 weeks. 3-D conformal radiotherapy was given concurrently using 50 Gy over 25 fractions, 6 fractions per week with another 10 Gy in 5 fractions as a local boost. An additional two cycles of chemotherapy was given after radiotherapy.
The patient developed severe radiation oesophagitis requiring parenteral nutrition support. His symptoms of dysphagia disappeared 1 month after treatment. Follow-up CT scan and OGD showed no evidence of recurrence. A CT scan 52 months after treatment (Figure 1b) showed complete radiological resolution of the disease. The patient is in remission and asymptomatic at 68 months post-treatment.

Case 2. A 43-year-old male patient presented with haematemesis and dysphagia. A CT scan done in August 2001 showed extensive disease in the oesophagus measuring 12 cm with a right paravertebral mass (Figure 2a). The patient was treated in a similar manner to Case 1 above, and he is completely symptom-free 4 months after treatment with resolution of most of the disease. The latest CT scan from February 2006 (Figure 2b) showed no evidence of recurrence.

Case 3. There is recent evidence to suggest that PET/CT can predict local control and survival[7] after chemoradiation, and may be used to select patients for definitive chemoradiation. To illustrate this, here is an example of a 56-year-old woman who presented recently with severe dysphagia. She was subsequently found to have squamous cell carcinoma with mediastinal lymphadenopathy (Figure 3a). She was treated with chemoradiation as before.
She is in complete remission according to a PET/CT performed 3 months after treatment (Figure 3b). This resolution of disease on PET/CT may predict local control without surgery.

Discussion. The standard treatment for inoperable or medically unfit patients with oesophageal carcinoma is combined chemoradiotherapy. This applies to squamous cell histology and also adenocarcinoma.[5,6] Complete pathological remission rates in the region of 40% can be expected. For resectable tumours, meta-analysis data suggested superior local control and survival with trimodality (chemoradiation followed by surgery) over surgery alone.[3,6] It is of note that the majority of patients in that study suffered from adenocarcinoma. Alternatively, adding surgery to chemoradiation may increase local control but the survival may not improve.[6] As most radiation or chemoradiation patients are either locally advanced or medically unfit, there is patient-selection bias in comparing surgical series. Palliative oesophagectomy should not be performed in patients with locally advanced disease or with distant metastasis because this group of patients can be treated effectively with either oesophageal stenting or chemoradiation.
While surgery remains the standard treatment for resectable early-stage oesophageal carcinoma in medically fit patients, chemoradiation can offer another option, especially for elderly patients or those with an advanced stage of disease.

Fig 1a. CT scan revealing an occlusive lesion at the mid-oesophagus level

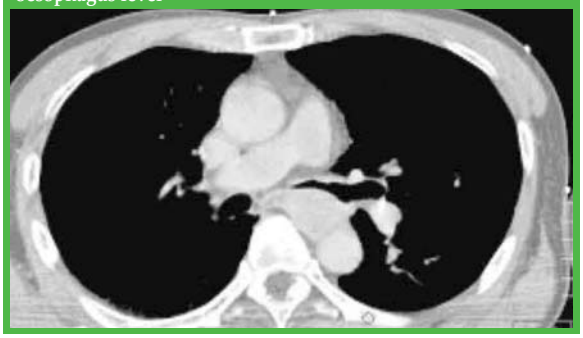


Fig. 1b. Repeat CT scan 52 months after treatment showing complete radiological resolution of disease

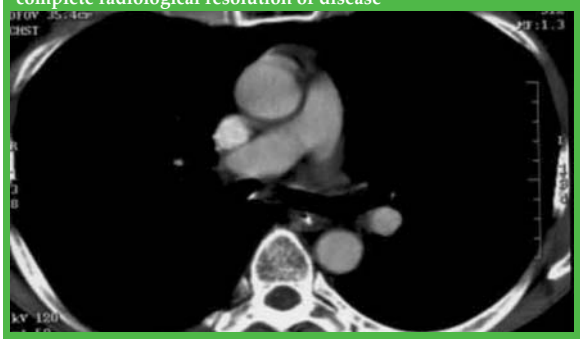


Fig. 2a. CT scan from August 2001 showing extensive disease in the oesophagus measuring 12cm with a right paravertebral mass

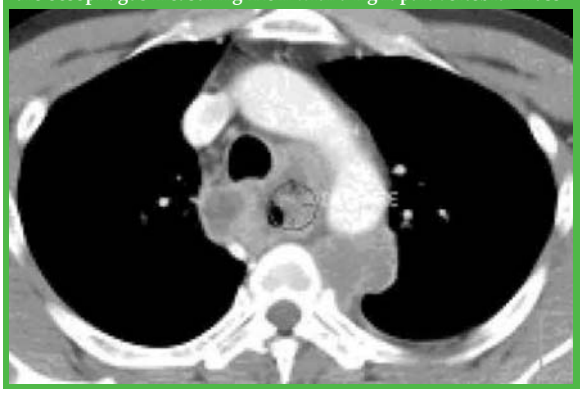


Fig. 2b. Repeat CT scan from February 2006 with no evidence of recurrence

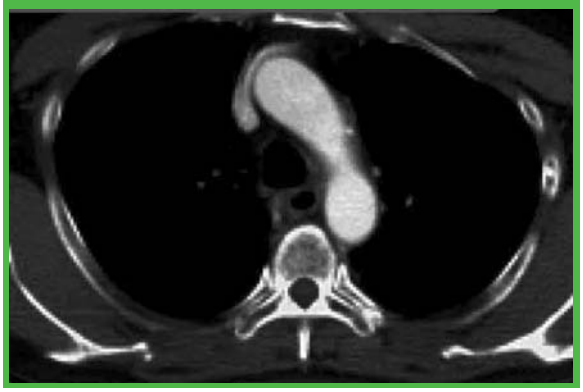


Fig. 3a. PET/CT image reveals squamous cell carcinoma with mediastinal lymphadenopathy

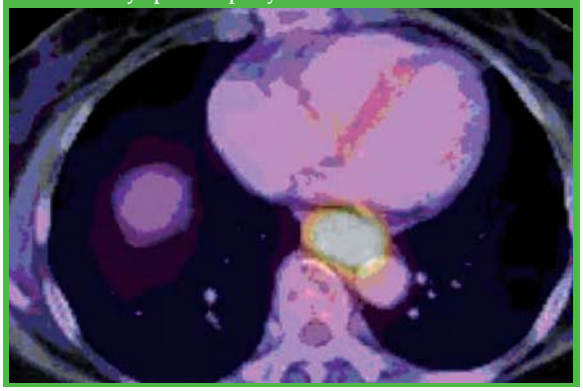
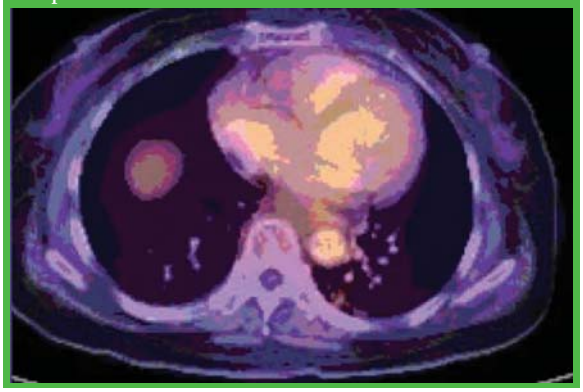


Fig. 3b. Repeat PET/CT done 3 months after treatment shows complete remission



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Pre-operative Chemoradiation for Advanced Rectal Cancer

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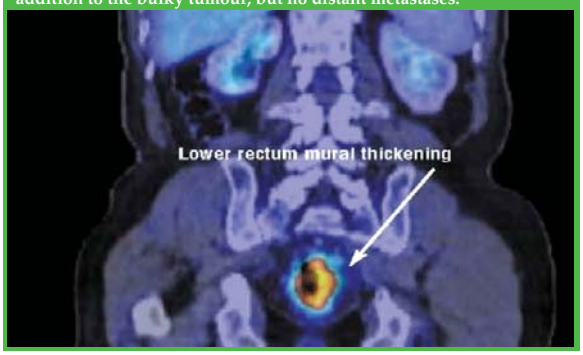
Introduction

There has been a growing trend for the use of pre-operative chemoradiation in the curative treatment of rectal cancer. The aims are to downstage the tumour, enable sphincter preservation in cancers situated in the lower third of the rectum, and possibly to increase the cure rate. Overall, about 15% of patients will achieve pathological complete response to the chemoradiation treatment prior to surgery, and another 60% of patients will achieve partial response. The former group usually has a very favourable long term outcome. Sphincter preservation is achieved in more than half of the patients who would otherwise have to undergo abdominoperineal resection. The following case history is one of the growing number of success stories.

History and investigations

A 71-year-old gentleman was diagnosed with histologically proven adenocarcinoma of the rectum in December 2003. The inferior border of the tumour was at 5 cm from the dentate line, and it was locally advanced, involving the whole circumference of the rectal wall. The tumour measured 7 cm in length. PET-CT scan showed enlarged para-rectal lymph nodes in addition to the bulky tumour, but no distant metastases (Figure 1).

Figure 1. PET-CT scan showing enlarged para-rectal lymph nodes in addition to the bulky tumour, but no distant metastases.



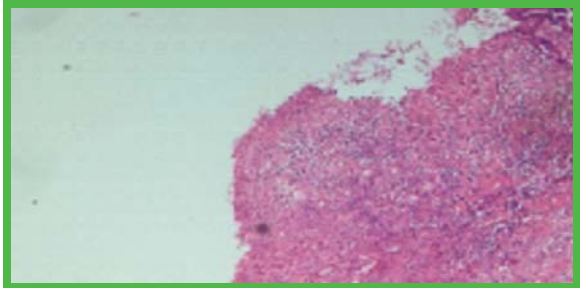
Management

The patient was referred for pre-operative chemoradiation. A total dose of 50 Gy over 25 fractions in 5 weeks was given to the pelvis by multiple beams. Concurrently, intravenous leucovorin and 5-fluorouracil (5FU) were given during the first 5 days and the last 5 days of the radiotherapy treatment.

The patient underwent a low anterior resection 6 weeks after completion of radiotherapy. During the operation, the surgeon could not palpate any tumour, and said he actually felt like he was operating on a disease-free person.

The pathology of the resected specimen showed an 8-cm-long shallow ulcer in the original tumour site. Microscopically, there were no residual carcinoma cells identifiable either in the rectum (Figure 2) or in the para-rectal lymph nodes. The patient has his sphincter preserved, with good function.

Figure 2. Pathology of the original rectal tumour site shows absence of residual carcinoma cells.



A Case of Complete Pathological Remission by Chemoradiotherapy in Inoperable Non-small Cell Lung Cancer

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Introduction

Inoperable non-small cell carcinoma of the lung has a poor prognosis. Despite the use of radical radiotherapy, the median survival has been about 9 months and the overall 5-year survival rate only 5%. Various methods have been tried including neoadjuvant chemotherapy followed by radiotherapy. However, evidence suggests that the use of concurrent chemotherapy and radiotherapy followed by surgery will offer the best local control and survival. An example of this treatment was reported at the Joint Oncology Conference on October 26, 2004.

History and presentation

A 45-year-old Chinese woman from Vancouver, Canada, was diagnosed with an inoperable adenocarcinoma in July 2003. She is a non-smoker but both of her parents had lung cancer. She presented with dry cough for 3 months with no haemoptysis, dyspnoea or weight loss.

Investigations

Chest x-ray showed a 2.5-cm mass in the left upper zone. Unfortunately, CT thorax showed an enhancing 3.5 x 3.4 x 3.3 cm mass with an irregular margin in the left upper lobe, which was adherent to the aortic arch, and also another adjacent cavitating 2.0 x 1.9 x 1.6 cm mass. There were multiple mediastinal lymph nodes up to 1.5 cm including AP window. The patient also had a PET scan confirming the extensive locoregional disease, but there were no distant metastases. She was seen by a thoracic surgeon and her tumour was considered inoperable.

Management

After detailed discussion with the patient and her family, the decision was made to use neoadjuvant concurrent chemotherapy and radiotherapy (Figure 1). Two cycles of Taxol (paclitaxel) at 175 mg/m2 + carboplatin at AUC 6 every 3 weeks was started from 30 July 2003 together with concurrent radiotherapy (6 fractions/week). A total dose of 56 Gy in 28 fractions was completed on 30 August 2003. There was no significant marrow toxicity or weight loss after treatment. However, the patient experienced moderate radiation oesophagitis.

Two weeks after treatment, a repeat CT scan showed significant reduction of the lung masses and the disappearance of the enlarged mediastinal lymph nodes.

As planned, a left pneumonectomy was performed 4 weeks after treatment and there was no adhesion encountered during the resection.

The surgical pathology showed extensive necrosis of the original tumour with no identifiable viable tumour cells (Figure 2). There was no tumour detected in the resected mediastinal lymph nodes.

After surgery, she received four cycles of Taxol/carboplatin as adjuvant therapy. Two months after chemotherapy, the patient experienced a sudden generalised seizure. The subsequent MRI showed three cerebral deposits (Figure 3), which were all successfully treated with stereotactic radiosurgery.

Outcome

The patient was well when last seen in January 2005.

Figure 1. Patient was treated using chemoradiotherapy before surgery. The primary tumour, the involved lymph node and subclinical disease were covered by the Planning Target Volume (PTV). The isodose lines are also shown.

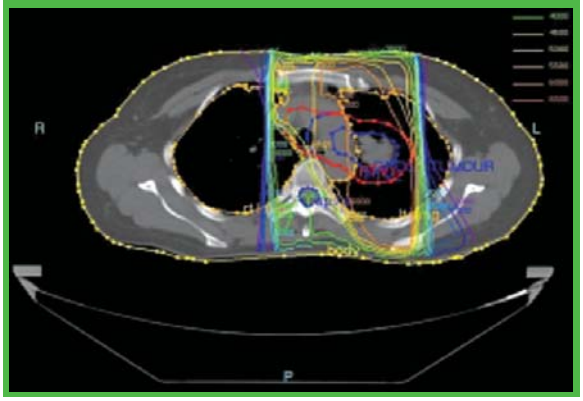

Figure 2. Histology of the resected tumour shows extensive necrosis with no identifiable viable tumour cells.

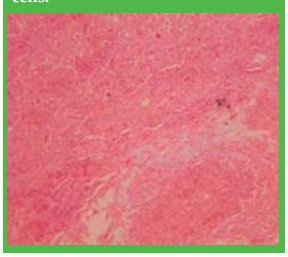

Figure 3. CT and MRI images showing the cerebral deposits, which were well covered by the radiosurgery treatment.