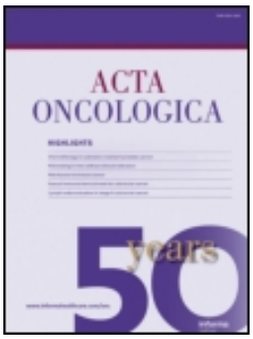

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Kalevi Pulkkanen, Tapani Lahtinen, Antti Lehtimäki, Michael C. Joiner & Vesa Kataja (2007) Effective palliation without normal tissue toxicity using low-dose ultrafractionated re-irradiation for tumor recurrence after radical or adjuvant radiotherapy, Acta Oncologica, 46:7, 1037-1041, DOI: 10.1080/02841860701280741

To link to this article: https://doi.org/10.1080/02841860701280741

Published online: 08 Jul 2009.

Acta Oncologica, 2007; 46: 1037–1041

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LETTER TO THE EDITOR

Effective palliation without normal tissue toxicity using low-dose ultrafractionated re-irradiation for tumor recurrence after radical or adjuvant radiotherapy

KALEVI PULKKANEN[1], TAPANI LAHTINEN[1], ANTTI LEHTIMÄKI[2], MICHAEL C. JOINER[3] & VESA KATAJA[1,4]

[1]*Department of Oncology, Kuopio University Hospital, Kuopio, Finland,* [2]*Department of Radiology, Kuopio University Hospital, Kuopio, Finland,* [3]*Department of Radiation Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, USA and* [4]*Department of Oncology, Vaasa Central Hospital, Vaasa, Finland*

To the Editor

Re-irradiation of local tumor recurrence after previous radical or adjuvant radiotherapy is often problematic because of the risk of high grade toxicity in normal tissues and inherent or acquired radioresistance of tumors. Using standard fractionation, re-treatment total doses remain low and responses are limited [1–7].

Several tumor cell lines, many of them considered radioresistant, have shown excessive low-dose hyperradiosensitivity (LD HRS) at fraction doses $\leq$0.5 Gy, followed by increased radioresistance at doses 0.5–1 Gy. Beyond 1 Gy, there is the usual downward bending survival curve with increasing dose [8–10]. Recovery of LD HRS after 3–4 hour interval allows delivery of successive small doses 3–4 times daily [11,12].

DNA double-strand breaks (DSBs) are considered as the prime lesions for potential cell death after radiation exposure [8]. The integrity of DNA is tightly monitored at several checkpoints in the G_1, S and G_2 phases, and damages are effectively repaired by a number of mechanisms [13,14], which to a large extent are regulated by the ataxia teleangiectasia mutated (ATM) protein [15,16]. It seems that using low doses of ionizing radiation, the activation of ATM and the function of its downstream target histone H2AX [17,18] is limited allowing the tumor cells harboring DNA DSBs to pass the second G_2/M checkpoint [14,19] and proceed into mitosis without being repaired [14,20–22]. However, recent data suggests that LD HRS is not a result from the failure of cells to recognize DNA DSBs due to the non-functional ATM [23]. Several other explanations, including local immune responses or tumor cell hypoxia, have also been proposed as possible mechanisms of LD HRS [24].

Based on the rationale of a high proportion of radiation-damaged G_2 phase tumor cells entering mitosis, together with a low proportion of cells in the vulnerable G_2 phase in normal tissues, we have used low-dose ultrafractionated radiotherapy (LDUF RT) in selected patients with a symptomatic tumor recurrence in the previously irradiated area to achieve effective palliation but minimal normal tissue toxicity.

Patients, methods and treatment outcome

The characteristics and tumor details, given treatments, clinical and radiological responses, and observed toxicity of 11 adult patients are described in Tables I–III. Full information of the experimental nature of the treatment and alternative treatment options was provided before patients' agreement to receive LDUF RT, and the ethical standards of the

Correspondence: Kalevi Pulkkanen, Department of Oncology, Kuopio University Hospital, FIN-70210 Kuopio, Finland. Fax: +358 17 172907. E-mail: Kalevi.Pulkkanen@kuh.fi

(Received 4 February 2007; accepted 12 February 2007)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860701280741

Table I. The characteristics of the patients with recurrent malignant tumors of the central nervous system, and the description of low-dose ultrafractionated radiotherapy, anti-tumor response, and toxicity.

Patient, sex, age, and tumor type	Prior chemotherapy regimens	Prior surgery	Prior radiotherapy	Interval to LDUF RT	LDUF RT	Symptom and its grade before LDUF RT	Clinical response after LDUF RT	Radiological response and its duration after LDUF RT	Toxicity	
									Acute	Late
#1 M, 33 years oligodendroglioma, grade II	0	2	31 ×1.8 Gy Total 55.8 Gy	9 years	90 ×0.5 Gy Total 45 Gy	Seizures (3) Headache (3) Motor neuropathy (2)	No symptoms	CR and no local recurrence at 2 years	No	No
#2 F, 40 years, oligodendroglioma, grade II	1	2	33 ×1.8 Gy Total 59.4 Gy	8 years	90 ×0.5 Gy Total 45 Gy	Seizures (3) Diplopia (3)	Seizures (2)	CR for 3 years and 8 months, then local recurrence	No	No
#3 F, 33 years, astrocytoma, grade III	0	3	33 ×1.8 Gy Total 59,4 Gy	8 years	90 ×0.5 Gy Total 45 Gy	Seizures (3)	Seizures (0)	CR for 4 years and 8 months, then local recurrence	No	No
#4 M, 47 years, oligoastrocytoma, grade III	1	2	30 ×2.0 Gy Total 60 Gy	18 years	102 ×0.5 Gy Total 51 Gy	Headache (3) Dizziness (3) Motor neuropathy (4) Fatigue (2)	Headache (0) Dizziness (0) Motor neuropathy (1) Fatigue (1)	PR at 6 months	No	No
#5 M, 42 years, cerebral neuroblastoma (PNET)	2	3	32 ×1.8 Gy Total 57.6 Gy	6 years	90 ×0.5 Gy Total 45 Gy	Seizures (3) Memory loss (3) Fatigue (2)	Seizures (0) Memory loss (3) Fatigue (2)	PR at 3 months, then progression	No	NR

LDUF RT = low-dose ultrafractionated radiotherapy; CR = complete response; PR = partial response.
NR = no referrals.

Table II. The characteristics of the patients with recurrent rectal cancer, and the description of low-dose ultrafractionated radiotherapy, anti-tumor response, and toxicity.

Patient, sex, age, and tumor type	Prior chemotherapy regimens	Prior surgery	Prior radiotherapy	Interval to LDUF RT	LDUF RT	Symptom and its grade before LDUF RT	Clinical response after LDUF RT	Radiological response and its duration after LDUF RT	Toxicity	
									Acute	Late
#6 F, 43 years, rectal cancer, T3N0M0	3	2	28 × 2.0 Gy Total 56 Gy	2 years	60 × 0.66 Gy Total 39.6 Gy	Tumor pain (4) Secretion from the natal cleft fistula (4)	Tumor pain (1) Secretion from the natal cleft fistula (2)	PR for 9 months, then local progression	No	No
#7 M, 60 years, rectal cancer, T2N0M0	2	2	28 × 1.8 Gy Total 50.4 Gy	1 year	83 × 0.5 Gy Total 41.5 Gy	Tumor pain (4) Secretion from the natal cleft fistula (4)	Tumor pain (2) Secretion from the natal cleft fistula (2)	SD for 3 months, then local progression and distant metastases	No	NR
#8 M, 62 years, rectal cancer, T4N1M0	3	1	25 × 2.0 Gy Total 50 Gy	4 years	99 × 0.5 Gy Total 49.5 Gy	Rectal discharge (3)	Rectal discharge (1)	SD for 12 months, then local progression and distant metastases	No	No

LDUF RT = low-dose ultrafractionated radiotherapy; PR = partial response; SD = stable disease.
NR = no referrals.

Table III. The characteristics of the patients with other type of recurrent tumors treated using low-dose ultrafractionated radiotherapy.

Patient, sex, age, and tumor type	Prior chemotherapy regimens	Prior surgery	Prior radiotherapy	Interval to LDUF RT	LDUF RT	Symptom and its grade before LDUF RT	Clinical response after LDUF RT	Radiological response and its duration after LDUF RT	Toxicity	
									Acute	Late
#9 F, 81 years renal cancer, T4NXM1	2	2	30 × 2.0 Gy Total 60 Gy (for lung metastasis)	6 years	60 × 0.6 Gy Total 36 Gy (for lung metastasis)	Dyspnea (3) Fatigue (3)	Fatigue (1)	PR for 10 months, then local progression	No	No
#10 M, 30 years, sacral osteosarcoma	1	1	35 × 2.0 Gy Total 70 Gy	5 years	60 × 0.5 Gy Total 30 Gy	Tumor pain (3) Motor neuropathy (3)	Tumor pain (3) Motor neuropathy (3)	PD locally and in metastases	No	NR
#11 F, 44 years, ductal carcinoma of the breast	3	1	27 × 1.8 Gy Total 48,6 Gy (for supra-clavicular metastases)	6 years	90 × 0.5 Gy Total 45 Gy (for supra-clavicular metastases)	Tumor pain (3) Lymphoedema (2)	Tumor pain (1) Lymphoedema (2)	SD at 6 months	No	No

LDUF RT = low-dose ultrafractionated radiotherapy; PR = partial response; PD = progressive disease; SD = stable disease.
NR = no referrals.

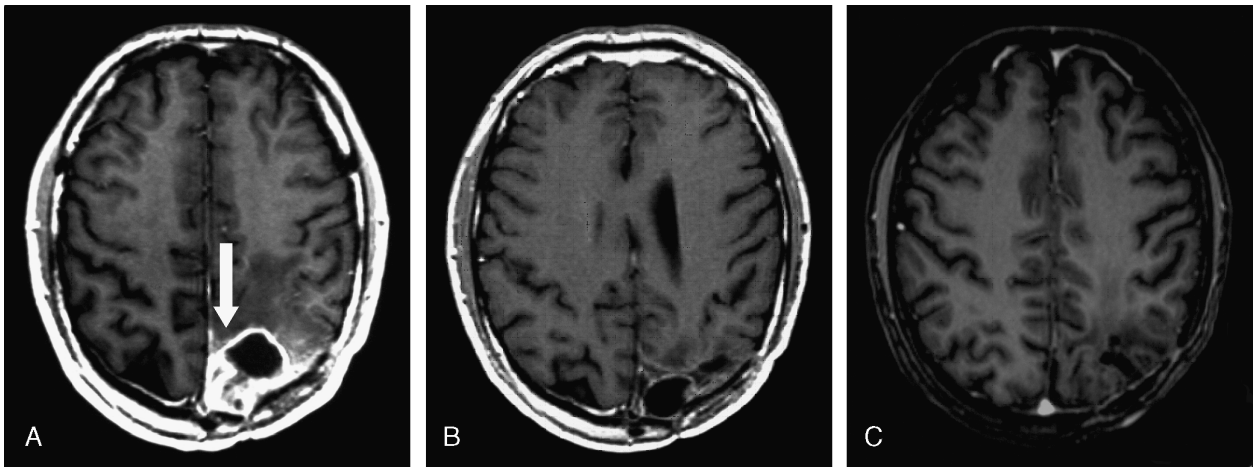

Figure 1. Imaging of the anti-tumor response of low-dose ultrafractionated radiotherapy. (A) A patient (Table I, #1) with a rapid recurrence of grade II oligodendroglioma (arrow) 4 months after the second operation and 2 weeks before LDUF RT. A complete response is seen (B) 6 months and (C) 2 years later. T_1-weighted contrast-enhanced MRIs.

Helsinki Declaration were followed. Clinical condition of the patients was graded according to the NCI common toxicity criteria (CTC), and tumor responses were evaluated using RECIST. Acute toxicity and late morbidity were assessed using NCI CTC and RTOG/EORTC scoring system, respectively. All patients were treated with three-dimensional conformal beam radiotherapy. Three fractions of 0.5 Gy (nine patients), 0.6 Gy (one patient), and 0.66 Gy (one patient) were given daily 4 h apart, 15 fractions per week. The total number of fractions per treatment varied from 60 to 102, the total radiation dose between 30 and 51 Gy, and the treatment time from 28 to 46 days. The interval from prior irradiation to LDUF RT varied from 1 to 18 years.

Five patients (#1–#5) had an intracranial malignancy (Table I). Prior to LDUF RT, all had undergone surgery at least twice due to a local recurrence, and three had received chemotherapy. LDUF RT caused no acute toxicity or late morbidity, and resulted in three complete responses up to duration of nearly 5 years (Figure 1). Also, a striking and long-lasting reduction of clinical symptoms was observed in every patient.

Three patients (#6–#8) had rectal cancer (Table II). All had received at least two regimens of chemotherapy, and two had been re-operated due a local recurrence. Despite multiple treatments, they suffered from local residual tumor growth causing severe pain and complicated fistulae in the gluteal and coccygeal region. Although large volumes (80% isodose volume 1265–2640 ml, including planning target volume) of pelvic region were irradiated, no toxicity related to re-irradiation was observed, and a clear relief of disabling symptoms, lasting up to one year, was achieved.

Regarding other type of tumors (Table III), an elderly patient with operated renal cancer and low respiratory function (#9) received LDUF RT for a large recurrent lung metastasis (field portals 10.5 $\times$ 12.0 cm) resulting in partial response and significant palliation of symptoms. Also, a patient with supraclavicular lymph node metastases from breast cancer (#11) experienced relief of pain, but a patient with osteosarcoma of the sacrum (#10) did not benefit from the treatment. Again, these patients did not present any radiation-related toxicity.

Conclusions

LD HRS has been demonstrated clinically effective in metastatic tumor nodules of skin [24]. However, this is the first publication analyzing toxicity and palliative efficacy of the LDUF RT in the treatment of recurrent tumors managed previously with surgery, chemotherapy, and conventional radical or adjuvant radiotherapy. Traditionally, palliative limited-field irradiation to a total dose of about 30 Gy is offered to these patients, if any therapy at all.

The total dose of external beam re-irradiation for primary brain tumors varies typically between 35–40 Gy with a fraction size of 1–3 Gy resulting in mean overall response rates of 40–50% [1–4]. However, these treatments have caused severe acute toxicity and a variety of late complications including profound neurological injury, increased intracranial pressure, and necrosis in 10–30% of the patients during a median survival between 9 and 36 months.

The re-treatment doses for rectal cancer have ranged from 30 to 36 Gy using a fraction size of 1.8 Gy or hyperfractionation with 1.2 Gy twice a day [5–7]. These studies have demonstrated marked response rates for local control and pain relief, and

survival extending up to 3 years. However, numerous treatment-related adverse events like diarrhoea, skin and mucosal reaction, abscess, small bowel obstruction, fistula, coloanal stricture, and ulceration have been reported. It is probable that a certain amount of these complications are also tumor-related.

It has been shown that only G_2 cells exhibit LD HRS [21] and therefore tumors with a high G_2 content, which are expected to have a low potential doubling time and high cell loss factor [25], should show more effect of reducing the fraction size. This could explain why the most significant benefit and anti-tumor response from LDUF RT was achieved in patients with malignant glioma.

The treatment schedule of LDUF RT is demanding for the patients, and increased labor and limited accelerator capacity restricts its use in daily practice. However, based on the experience of our small series of patients, LDUF RT is a safe option for effective palliation with minimal toxicity in selected patients with locally recurrent tumors after conventionally fractionated radical or adjuvant radiotherapy.

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