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500 kHz hyperthermia assisted HDR brachytherapy in the treatment of recurrent cervical and endometrial cancer in previously irradiated fields

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Summary

Background The biological effectiveness of elevated temperature (hyperthermia) on cancer cells is a well documented issue. Nevertheless, it is still not widely used in clinical practice, mainly due to technical difficulties. The main limiting factor is the protection of healthy tissue during the hyperthermia procedure. Hyperthermia, used as an adjuvant treatment with brachytherapy, provides the possibility of lowering total radiation doses, without reducing biological effects.

Aim The aim of this work was to present the advantages of using 500 kHz hyperthermia in HDR brachytherapy of cervical & endometrial cancer.

Materials/Methods Hyperthermia procedures were performed in 8 endometrial cancer patients and 2 cervical cancer patients with early recurrent local disease in previously irradiated areas. One or two interstitial hyperthermia procedures were performed using rigid metal needles, both for brachytherapy and temperature elevation. The total radiation dose was 30 Gy, delivered in 3 or 6 Gy per fraction. In the case of 3 Gy per fraction, a scheme of two fractions per day, separated by at least 8 hours, was used. The total treatment time ranged from 5 to 14 days. Hyperthermia was performed concurrently with brachytherapy.

Results During the treatment, no acute reactions were observed. In each case, tumour regression over 50% was noted. During the 3 to 14 month follow-up period, complete vaginal tumour regression was seen in 8 of 10 cases.

Conclusions 500 kHz hyperthermia assisted interstitial brachytherapy can be regarded as effective and safe procedure, especially when applied as secondary (salvage) treatment. More cases and longer observation time are needed to make definite conclusions.

Key words **cervical cancer • endometrial cancer • brachytherapy • secondary radiotherapy**

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Background

Despite diagnostic and therapeutic progress, cervical cancer still has one of the worst epidemiological indices in Poland. Data analysis for the year 2000, has shown a morbidity level of 6.8% and a mortality level 5.4% for all malignancies. During the same period, 3597 new cases of cervical cancer were diagnosed and 1987 deaths were recorded as being caused by this disease [1]. In quite a large proportion of patients, because of the advanced clinical stage of the disease (IIB-IIIB according to FIGO), the treatment of choice is radiotherapy or radio-chemotherapy with intent to-treat. To reach the optimum dose distribution, the accepted standard is to supplement the dose delivered during external beam radiotherapy, with intracavitary brachytherapy [2]. The epidemiological indices for endometrial cancer, during the same year were 3276 (6.2% of all malignancies), and are not so pessimistic. During the year 2000, a total of 808 deaths caused by endometrial cancer were noted, which accounts for 2.2% of all deaths caused by these malignancies. Better results of therapy in this case are mainly owing to less advanced disease which gives the possibility for radical surgical treatment (and eventual adjuvant external beam or brachytherapy) [3]. In either of the above mentioned tumour sites, there may be some problems with patients suffering from relapse in a previously irradiated field. Co-exisitng conditions and the impossibility of injury avoidance, often exclude surgical treatment, while the tolerance dose of critical organs makes secondary irradiation impossible. Improved biological effectiveness from elevated temperatures (hyperthermia) on cancer cells and the potential of its association with radiotherapy is a well known issue. Nevertheless it is not used widely enough in oncological practice. The main limiting factors are technical difficulties regarding hyperthermia procedures. The problems are connected with limited capabilities in obtaining therapeutic temperatures (>42.5°C) inside the tumour while maintaining healthy tissue protection. Hyperthermia, used as a complementary treatment to radiotherapy provides the possibility to deliver lower doses with the same biological effects. Interstitial brachytherapy may enhance this phenomenon by reducing the irradiated volume and makes it possible to deliver simultaneous hyperthermia to the irradiated tissues via the same applicators. A unique therapeutic HT-2 set, used in the Centre of Oncology, allows the practical use of hyperthermia in the treatment of cervical and endometrial cancer [4].

Materials

Hyperthermia procedures were performed in 10 patients: 8 endometrial cancer cases and 2 cervical cancer patients with early recurrence in a previously irradiated field. Hyperthermia was combined with interstitial HDR brachytherapy. Patients were aged between 46 and 75 years (average 65). All the patients underwent, prior to recurrence detection, primary post-operative, external beam irradiation (box technique, 46Gy/23fr) with the addition of vaginal cuff HDR brachytherapy (2–3 × 7,5Gy/fr/0,5cm from the applicator surface).

Methods

An HT-2 set with a 500 kHz frequency generator [4] was used. One or two interstitial hyperthermia procedures were performed, using rigid metal needles for an HDR Ir-192 source (Gammamed 12i) and for energy transmission. The total dose was 30 Gy, dose per fraction 3 or 6 Gy, and total treatment time was from 5 to 14 days. In the case of 3 Gy per fraction, irradiation was performed twice daily with an interval of at least 8 hours. Dose distribution calculations were based on x-ray needle localizations using the Abacus computer planning system. The dose was specified as 0.5–0.7 mm from the needle surface. The irradiated volume ranged from 25 to 50 cm^3 (average 30 cm^3). For this group of patients, thanks to the mobility and the compact size of the HT-2 set, unique application of brachytherapy during the hyperthermia procedure was possible (after the therapeutic values of the temperatures were obtained, brachytherapy was started, without interruption of the hyperthermia procedure). In each case, in order to avoid the thermoresistance effect, the hyperthermia procedure was performed at 48 hours intervals. The total treatment time was 45–60 minutes and included at least 45 minutes with temperatures at up to 46–49°C.

Results

Early sequelae, which may have caused interruptions in treatment, were not observed. In every case, irradiation reactions appeared as erythema with superficial subsidence of the epithelium and intensified mucous secretion. Rectal and bladder reactions were observed in 6 patients but were limited to grade I, according to the EORTC/RTOG scale, and were cured spontaneously. Follow-ups were performed one month after treatment and every 3 months thereafter. Post-irradiation reaction

symptoms disappeared 2–3 months after conservative treatment (local steroids, vessel wall protectant / oxerutin / anti-infamatory agents / diclofenac). No late side-effects were observed. During the follow-up period of 3 to 14 months, complete vaginal tumour regression was confirmed by clinical examination in 8/10 cases. In two cases no regression was seen. In one case of cervical cancer, a tumour of 4 cm was observed in CT scans before treatment. Complete regression of the tumour was seen after treatment. This effect lasted for 10 months. This patient died as a result of sigmoid perforation, followed by peritonitis. From the surgical point of view, the observed lesions were located outside the re-irradiated volume. The perforation was owing to sigmoid occlusion caused by adhesions. In a second case, after 5 months follow-up with complete regression, vaginal recurrence (outside the re-irradiated field) and pulmonary metastases were detected. In this case, chemotherapy according to the PAC scheme (cis-platin, adriamycine, cyclophosphamide) was performed. Tumour stabilization was observed.

Discussion

The treatment of early recurrence in previously irradiated fields is not an easy task. The possibilities for surgical treatment are often limited because of the impossibility of obtaining optimal margins without serious injury to the patient (often colpectomy or ureterotomy). Further irradiation is often impossible owing to risks in exceeding the tolerance doses for healthy tissues. The only alternative method is chemotherapy, which cannot be regarded as radical treatment. It seems that the most interesting possibility for this group of patients is the application of hyperthermia as a method for strengthening the effects of radiation therapy [5]. Several recently published papers show a higher index of clinical effectivness after incorporating hyperthermia into radiotherapy. Among the most relevant of these are the results of the "Dutch Deep Hyperthermia Group". This was a prospective, randomised, multi-centre study based on the treatment results of 358 patients with cervical, rectal or bladder cancers. In this group, the 114 patients with cervical cancer were divided into two subgroups – 58 patients received radiotherapy and hyperthermia and 56 patients received radiotherapy alone. Local control rates were 61% and 41% with 3-year survival times being 51% and 27% respectively and being statistically significant. In the subgroup of patients with rectal cancer (143 patients) no statistically relevant difference was observed. Again, the local control rates were respectively 16% and 8% with 3-year survival times of 22% and 13% respectively. For the 101 patients with bladder cancer respective values were 42% versus 33% and 28% versus 22%[6]. It is very important to note that these results were obtained using "external heating" which is not so effective as intracavitary heating due to treatment intolerance and a lower range of temperatures.

In a randomised trial by Harima et al, assessing the concentration of Bax and Bcl-2 proteins in irradiated cervical carcinoma cells, significantly different protein concentrations were found when treatment by hyperthermia and radiotherapy was compared with radiotherapy alone. This was positively correlated with the percentage of complete tumour regression (83.3% in the hyperthermia combined group vs. 52.6% in the radiotherapy alone group). A negative correlation was observed with lack of response (5.6% vs. 21.1% respectively) [7].

Vasanthan et al. found no benefits from the addition of hyperthermia to radiotherapy in cervical cancer patients. It should be pointed out that the temperatures achieved in this study were in many cases significantly lower than needed minimum of 42.5°C [8]. Being multi-centered, this study included a very limited number of patients from each institution (1–27) and irradiation was performed in a non-uniform manner. The hyperthermia procedure was performed using different machines and using different protocols. Temperature measurements were not performed in more than 50% of the hyperthermia sessions. With respect to the increasing efficiency of radiotherapy, limitation of the total dose and avoidance of late sequelae are possible. An interesting observation was made by Van der Zee et al. [9] while evaluating post-irradiation injuries in post mastectomy breast cancer patients, treated for scar recurrence. Two adjacent regions of the thoracic wall were irradiated with the same dose. The difference between these areas was the addition of simultaneous hyperthermia to irradiation therapy in one field. As a result, significantly fewer signs of telangiectasia were observed in hyperthermia treated fields. Authors associate this with faster sub-lethal injury repairs to intraepithelial cells damaged during irradiation. In their study, Li et al. [10], treating breast cancer patients with recurrence, confirmed a higher percentage of complete remissions in previously irradiated fields when hyperthermia was added. Even significantly lower doses (43 Gy in radiotherapy + hyperthermia

group vs. 59.5 Gy in radiotherapy alone group), were more effective when hyperthermia was applied. In a recently published paper, Kouloulias et al. showed a higher sphincter preservation rate (95.8% radiotherapy + hyperthermia vs. 68.0% radiotherapy alone) when hyperthermia was added to the standard radio-chemotherapy of anal cancer patients [11].

With respect to the necessarily high radiation doses used in gynaecological malignancies, hyperthermia provides a means to limit radiation induced injuries. This fact is crucial in the case of re-irradiation. Studies with practical hyperthermia application, performed over several years at Centre of Oncology in Warsaw [4,12], confirmed its biological effect and proves its practical usefulness. In particular, simultaneous interstitial brachytherapy and hyperthermia allows us to take maximum advantage of the combination of both methods [13,14]. To date, however, the results presented above refer to a small group of patients with relatively short follow-up. Nevertheless, on this basis we may take advantage of the therapeutic potential of simultaneous hyperthermia and radiotherapy.

Conclusions

A 500 kHz hyperthermia assisted interstitial brachytherapy can be regarded as effective and safe procedure, specially when applied as secondary (salvage) treatment. More cases and longer observation time are needed to make definite conclusions.

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