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# Radiotherapy in combination with simultaneous intra-arterial chemotherapy (RADPLAT) in patients with advanced head and neck cancer

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# Summary

A particular challenge for both laryngologists and oncologists is presented by the fact that treatment of patients in advanced stages of cancer disease, in whom either combined therapy (surgery and adjuvant radiotherapy) or radiotherapy alone have been applied, is associated with highly dissatisfying results. Clinical trials exploring the application of chemotherapy combined with simultaneous radiotherapy are arousing greater interest. This is because the results of recently published randomised prospective studies and meta analyses show improved loco-regional results of this treatment strategy, which in turn improves overall survival. Cytostatic drugs used in conjunction with radiotherapy have many functions but, above all, their purpose is to intensify the effects of irradiation which, in such treatment schemes, is the leading method. One of the basic factors limiting the application of such strategies is the problem of how to limit the toxicity from one side, while administering a sufficiently high dose of cytostatics, and to continue without any gaps the course of radiation from the other. A problem associated with combined therapy is how to ensure the highest concentration of cytostatics is in the malignant tumour. The need to break through both of these limiting factors has become the subject of intensive research. One of the possible solutions to these problems is the simultaneous application of irradiation in combination with selective intra-arterial chemotherapy. To date, final results are still unavailable from phase III clinical trials which are investigating this treatment method. Presented in this paper are the advantages and disadvantages in the treatment strategy called the RADPLAT programme. The RADPLAT programme is characterised by great local effects, somewhat lesser regional effects and still lesser effects in the treatment of micro-metastases. Research is continuing, in order to find methods for the improvement of treatment results, with a view to reducing the risks of distant metastases and/or regional treatment failures.

Key words

head and neck cancer • radiochemiotherapy • intra-arterial selective chemotherapy • RADPLAT

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### BACKGROUND

Current oncology of the head and neck cancer is very often faced with a challenge; how to treat advanced tumours. Such tumours may be neighbouring structures important to life (large arteries, cranial nerves) and may be characterised by their closely defined surgical limitations. Despite this, surgery supplemented by postoperative radiotherapy remains the basic form of the treatment of patients in advanced stages of the head and neck cancer. However, because of poor efficacy and significant increases in side effects, research in this area has intensified worldwide in order to find more efficient methods of treatment [1,2]. Presently, one of the area of research which are arousing hope is combination radiotherapy and chemotherapy, and the greatest interest is concerning the concurrent application of radiotherapy and chemotherapy. Recently published results from prospective randomised trials and meta-analyses show that the greatest effects are in local treatments and in improvements to survival among patients treated by combined therapy (combined radio-chemotherapy), relative to radiotherapy alone [3,4]. Above all, the combined radio-chemotherapy strategy is aimed at intensifying the local effects of radiotherapy and, to a lesser degree, at reducing the number of cancer cells remaining beyond the irradiated volume (distant metastases). This results from the fact that in tumours of very advanced stages, destruction of the primary tumour and metastases to the lymphatic tissues of the neck is a basic condition for obtaining a cure. However, later during follow-up the problems of distant metastases and further second primary tumours may arise.

One of the basic factors limiting the use of combined radio and chemotherapy is the high level of toxicity associated with this treatment strategy. Such treatment may lead to limiting the dose of cytostatic drugs, or on the other hand may require that the radiation course to be prolonged [5,6]. One of the most important factors influencing the results of cytostatic treatment is attainment of the optimal concentration of the drug in the target cells. It is commonly assumed that the higher concentrations of the drug within the tumour cells, the greater the cytotoxic effect will be. One method of treatment which attempts to meet these expectations is the concurrent application of radiotherapy with selective high-dose of intra-arterial chemotherapy. Despite a four decade history of intra-arterial chemotherapy in the treatment of head and neck cancer, it is only with recent improvements to angiographic techniques that are relatively safe intra-arterial application of the drug to the immediate surroundings of the malignant tumour has become possible.

The RADPLAT programme combines high dose intra-arterial cisplatin application into the surroundings of the tumour with concurrent radiotherapy. It should be noted that the cisplatin doses given in the RADPLAT programme are much higher than those used in intra-venous delivery. In order to obtain a high concentration of cytostatics in the tumour, the drug is delivered directly via a catheter inserted into the arteries supplies the drug into the tumour using angiography. For the purposes of limiting the systemic effects of cytostatic drugs on healthy cells, while the cisplatin is being delivered arterially, thiosulphates are given intravenously, as they act as neutralisers of the cisplatin.

The RADPLAT programme represents an alternative to the commonly applied method of venous delivery of cytostatic drugs in the treatment of head and neck cancer. The first attempts at applying the treatment mentioned above showed that there existed the possibility of therapy to patients whose reached an inoperable stage [7–10]. The basic cytostatic drug used in combination with radiation is cisplatin. The key to obtaining maximum therapeutic effect is to deliver a high dose of drug to tumour cells [11]. Some factors limit the possibilities of increasing the dose of cisplatin and it is first necessary to determine the degree of toxicity to the renal and myeloid systems. Intravenous doses greater than 50mg/m<sup>2</sup> may be toxic to the renal, though use of lower doses is associated with poor therapeutic effect [12]. Careful control of hydration allows us to increase the dose of cisplatin to  $125 \text{mg/m}^2$  which results in improved treatment effects, though further increases in dose are limited by the onset of side effects.

The results of clinical trials in the treatment of head and neck cancer patients show that the highest percentage of response is obtained when cisplatin and radiation are applied simultaneously. At the same time, a clear relationship between therapeutic effects and the applied dose of cisplatin has been shown. Because of this, in 1996, Robbins and colleagues proposed treatment by the RADPLAT method, which combines intraarterial chemotherapy with simultaneous radiotherapy for the treatment of patients with advanced cancers of the head and neck. It should be noted, however, that localisation of the tumour within the head and neck region is an exclusive requirement when planning treatment by this strategy.

### A GENERAL OUTLINE OF TREATMENT ACCORDING TO THE RADPLAT PROGRAMME

### Radiotherapy

The above radiotherapy programme is realised in a conventional strategy of fractionation (1.8– 2.0Gy/day) up to a total dose of around 70Gy to the tumour and lymph nodes metastases. In clinical practice, modern radiotherapy techniques (IMRT) may allow for an improvement in the sparing of healthy tissue, which could be unusually important because of the need to reduce the side effects associated with simultaneous radiochemotherapy. It must be underlined that toxicity in healthy tissues is often a limiting factor in obtaining a response to treatment [13,14].

### Angiography

Angiography is performed according to Seldinger's method, via the arteries below the inguinal ligament. A metal guide measuring between 0.25 and 0.35 is inserted into the artery via a Seldinger needle. Using the guide, a catheter with a haemostatic valve is introduced to the femoral artery. Through the existing catheter, another is inserted for the selective catheterisation of branches of the aortic arch. For the purpose of identifying pathological vascularisation, selective angiography of the internal and external carotid arteries is performed. Angiography is carried out with the help of automated syringes loaded with non-ionic contrast medium (most frequently Omnipaq 300, Nycomed) and a solution of physiological saline in 50:50 proportions. The contrast medium is delivered selectively in volumes of 8 to 10ml at a rate of 4–6ml/s. After completion of the investigation and removal of the catheters, local pressure is applied to the area of the femoral arteries for 2 to 6 hours using a special pressure dressing. The patient remains lying down for the following 24 hours.

### Chemotherapy

Cisplatin is given within 1 hour of completing irradiation. For tumours which do not cross the midline of the body a single inlet to one carotid artery is recommended, while in the case of tumours which cross the midline, inlets in both carotid arteries are used. Cisplatin is given arterially at a dose of 150mg/m<sup>2</sup> over 3 to 5 minutes with simultaneous intravenous delivery of sodium thiosulphate at a dose of 9g/m<sup>2</sup>. All patients receive 4 courses of cisplatin during irradiation on days 1, 8, 15 and 22 or on days 2, 9, 16 and 23 of radiotherapy.

Chemotherapy details:

- 1.Dexamethazone 4 mg (iv) the evening prior to treatment.
- 2.Hydration prior to therapy: 1 litre 5% dextrose +20mEq KCL+ 2g MgSo4 for 2 hours before delivery of cisplatin.
- 3. Cisplatin at a concentration of 1mg/ml given by automated arterial pump at a rate of 1–2ml/second.
- 4. Sodium thiosulphate  $(9g/m^2 \text{ in } 200 \text{ ml distilled})$ water, given intravenously during a period of 15–20 minutes, simultaneously with cisplatin, and followed by a dose of  $12g/m^2$  continued for the following 6 hours (12g w 1 litre of distilled water and infused at a rate of 167 ml/min).
- 5.Hydration after therapy: after receiving thiosulphates the patient is given 1 litre of 5% dextrose +20mEq KCL.
- 6.Antiemetic drugs are given in accordance with the decision of the physician in charge, and local practices.

Dose modification is carried out in the case of:

- granulocyte count (PMN) >1.5×10<sup>9</sup>/l,
- platelet count  $>75 \times 10^9/1$ ,
- renal creatinine clearance >50ml/min,
- symptoms of stage II neurotoxicity,
- hearing loss greater than 20dB.

### The University of Tennessee, Memphis, USA

Robbins and colleagues [11] published the results of a phase I clinical trial (toxicity assessment) which assessed the arterial application of cisplatin in patients with cancers of the head and neck. The maximum tolerable dose (MTD) which could be delivered arterially, according to those authors, amounted to  $150 \text{mg/m}^2$ /week applied 4 times at weekly intervals. The authors noted the significant number of cases with complete or partial response (86%) and, in group of patients being treated for relapse, this rate is 63%. The results of *in vitro* studies show a dependency between the concentration of the cisplatin and the strength of the cytotoxic effect on malignant cells which, among other factors, gave us the possibility to explore the idea of high dose chemotherapy in clinical practice.

Further evaluation encompassed 213 patients who were enrolled into a phase II of study. In  $\frac{1}{3}$  of these patients it had not been possible to perform initial surgical treatment due to significantly advanced disease process (28.6% - clinical stage III, 71.4%)- clinical stage IV) while treatment according to the RADPLAT program allowed the attainment of complete regression in 91% of cases of primary tumours and in 61% of patients with metastatic disease to the neck. In the cases of 17 patients a partial regression was observed, 12 required salvage therapy, and in only 3 the treatment was of a radical intent. General toxicity of the treatment was fairly high, specifically toxicity grade III or IV mucositis which was observed in 56 patients. Haematological toxicities of the same degree were seen in 17 patients, neurological complications were observed in 9, and cardiological complications were noted in 8 patients. Actuarial 5-years overall survival for the whole group was 38.8%.

Additional analyses in the year 2001 showed that the patients most at risk of distant metastases are those with tumours localised in hypopharynx and those with massive local metastases to the neck lymph nodes. After follow-up the patients for many years the authors concluded that patients treated according to the RADPLAT programme:

- had a poorer prognosis if the tumour was located in the lower part of pharynx,
- had a significantly worsened prognosis in the event of massive metastasis to the neck lymph nodes,

• require closely cooperation by a multidisciplinary group with special attention being paid to the likely need for salvage therapy to be quickly applied in a significant proportion of patients.

The RADPLAT programme was also tested on small groups of patients with advanced tumours of the base of the skull, tumours of the neck in the N3 stage, and tumours of the nasal sinuses. A general summary of the results of treatment shows the programme has encouraging results in these localisations. It is also worth noting that the RADPLAT program is highly effective in patients with infiltration of the bones (T4). Complete responses in the cases amount to 66.7%, and show an actuarial 2 year overall survival of 46.3%; (95% CI: 30.3–62.3%) [15].

One of the most important purposes of current studies under the RADPLAT program is to identify predictive factors for this form of therapy, for the purposes of defining patient qualification criteria for this type of treatment. In an analysis undertaken by van der Broek and co-workers, factors such as the volume of the primary tumour, the volume of lymph node metastases, total volume of the tumour plus lymph nodes, localisation of metastases in the lower levels of the neck, low Hb level, large losses in body mass prior to treatment, and unilateral arterial cisplatin therapy were studied, though only the volume of the primary tumour and unilateral application of cisplatin showed a negative effect on patient survival [16]. Similarly, Doweck et al. [17] confirmed that the volume of the tumour is the strongest prognostic factor among patients treated according to the RADPLAT programme.

Another particularly important area of study is the assessment of quality of life for patients after completion of therapy. What is obvious is that efficiency of the RADPLAT programme is comparable with simultaneous intravenous chemotherapy and radiotherapy programms, and comparison leads to a very significant finding. To date, studies comparing the two methods of treatment have shown no difference in the quality of life of patients who have completed the therapy [18].

In any case, in squamous cell carcinomas of the head and neck, distant metastases do not represent a general negative indicator for poor response to treatment, it is in advanced stages of disease, and particularly in the case of massive metastasis to the cervical lymph nodes that remote metastases begin to take on significance. Also associated with this is the use of highly selective therapy, such as introducing drugs to specific arteries so that the maximum possible dose will be delivered to the tumour while a minimum will be delivered to the surroundings (healthy tissue) leading one to question the effects of such treatment strategies on the frequency of systemic failure. According to Doweck and colleagues [19], who observed these patients, treated using the RADPLAT method, those at the greatest risk for non-responsiveness to the system are cases with metastases to many levels of the neck and those with tumours localised in the hypopharynx. Among patients with clinical parameters other than those described above, results of treatment by the RADPLAT programme are likely to show less effectiveness.

# REGRESSION OF TUMOURS OF THE NECK AND RADPLAT: THE ROLE OF SURGERY

Close cooperation with head and neck surgeons is of vital importance. This is because of the fact that, in patients who fail to attain complete regression of the lesion in the cervical lymph nodes, it will be necessary to undertake surgical salvage treatment at the completion of radiotherapy. This is important because a lack of control in inaccessible regions remains a key factor for lack of response to therapy among patients who have undergone treatment according to the RADPLAT programme. Surgical salvage therefore represents a key element in the treatment protocol. This underlines the need for interdisciplinary surgeons, who are involved in qualification of patients for the programme, support during radio-chemotherapy course, and during the follow-up, which is when salvage surgery may be required.

# The Netherlands Cancer Institute, Amsterdam, Holland

In 1997 this Dutch centre adapted the RADPLAT programme for use in a phase II clinical trial, according to an identical protocol to that proposed by Robbins and colleagues. The Dutch researchers offered this form of treatment to patients for whom surgical operations were impossible owing to advanced stage of the primary tumour or the presence of massive metastasis to the lymph nodes. Out of 73 patients who qualified for analysis, 88% showed complete remission. Two year disease free survival and 2 year overall survival without symptoms of disease was noted in 65% and 45% respectively. The authors observed that

though the treatment was typically well tolerated, the procedure was associated with 1 death and that 17% of patients showed grade IV haematological toxicity symptoms. Aside from haematological symptoms, no other grade IV toxicity was observed [22]. Encouraged by the good results of treatment with good tolerance for the programme, the authors decided to carry out a full evaluation in the phase III randomised clinical trial (**RADPLAT vs. intravenous cisplatin + simultaneous radiotherapy**). This study is currently in the enrolment phase in 4 Dutch centres. At this point it should be pointed out that our centre in Poznan has also accepted the invitation of the Dutch researchers to take part in the trial.

### The George Washington University, Washington, USA

A study using a RADPLAT programme was begun in this centre in 1994 under the leadership of Wilson. However, the treatment scheme differed from that proposed in Memphis and Amsterdam. The existing programme was modified in the following manner: the treatment was carried out in a sequential manner, wherein the first phase was the application of arterially cisplatin at a dose of 150mg/m<sup>2</sup>/week for four weeks (neoadjuvant chemotherapy) after which radiation treatment was begun. On the basis of observations of a group of 58 patients, Wilson and colleagues [21] came to the conclusion that their treatment scheme (arterial neoadjuvant chemotherapy and radiotherapy) allowed a larger proportion of patients to maintain systemic function while simultaneously maintaining good tolerance to the treatment. From the practical point of view, it should be noted that the total treatment time from the first day of chemotherapy to completion of the course of radiotherapy is significantly longer than that of the classic RADPLAT programme. Besides that, the size of the study group did not allow for the extraction of results which may provide strong evidence. It should be noted that one of the underlying ideas of the programme is the intensification of therapy (dose/time) which, being modified in the programme as proposed by Wilson, has an effect on subsequent plans.

### Modifications to the RADPLAT Programme

### Pento-RADPLAT

Intensive treatment, such as that proposed in the RADPLAT programme, causes a significant number of patients to develop skin fibrosis. That being the case, among patients treated with irradiation and chemotherapy (in stages of advancement N2-N3), surgical procedures are carried out to remove the "remaining" metastatic nodes. For the purposes of limiting of the intensity of these fibrosis symptoms, authors have proposed to introduce pentoxyphyllin from the first day of radiation treatment in doses of 400mg given four times daily. This treatment was continued during follow-up several following months. A comparative analysis of two groups of patients was undertaken. The results showed that the patients given the prophylactic drug develop fibrosis (stage 0-II) in 60% of cases, while those who did not receive treatment developed fibrosis in 80% of cases. Similarly, the scale of grade III and IV complications was reduced among patients treated with pentoxyphyllin: 20% among those taking the drug vs. 40% among those who did not receive the treatment. It should be noted that these initial results, with regards to the use of pentoxyphyllin, indicated that it may be possible to make use of such procedures and further study is required.

### Neo-RADPLAT

The treatment of patients with advance tumours (T2 and T3) localised in the oral cavity and in the mid-portion of the throat remains problematic in that, to date, initial surgery is still associated with a significant reduction in the quality of life. This problem resulted in the concept of preoperative radiotherapy using doses up to 50Gy with simultaneous intra-arterial cisplatin chemotherapy (Neo-RADPLAT). After this initial treatment, patients in whom a complete remission cannot be obtained may be offered a "conservative" RADPLAT programme which frequently takes the form of removal of the tumour. What is worth noting here is the fact that complete remission after simultaneous radio-chemotherapy may be observed in as many as 75% of all patients treated [10]. That being the case, it seems very important to continue testing this type of modification to the RADPLAT programme.

### Multi-RADPLAT

Treatment according to the RADPLAT programme requires a high level of organisation and qualified personnel, which is why, in Poland, after completing the phase III study mentioned earlier, there is likely to be a delay in dissemination of the technique as a routine means of treatment. Eden In countries such as the United States, routine treatment according to the RADPLAT programme may cause organisational problems. This being the case, it may be that provision of this form of therapy in typical oncology centres may be impossible. Because of such problems, and In order to determine the potential for introducing the RADPLAT programme to routine therapies in clinical practice, a study was proposed which would include 11 selected American centres (3 with experience with RADPLAT and 8 with no experience). This study was realized in the form of the clinical trial RTOG 9615 which was carried out between 1997 and December 1999. Sixty-seven patients were enrolled: all patients were in stage IV and were located in the oral cavity, the oropharynx or larynx. In the initial findings of RTOG 9615, it was noted that 3 or 4 courses of cisplatin could be administered without harm in 84% of the cases. Among the patients studied, early toxicity from treatment was as follows: stage III=45%, stage IV=35% and stage V=3%. The greatest problem was the occurrence of mucositis of grades III and IV. Such problems were noted in 47% and 10% of patients, respectively. Centres with experience in treatment according to the programme recorded grade IV toxicity in 14% of patients while centres with no previous experience observed such toxicity in 47%. Two year disease free survival among the whole group amounted to 46% and total survival to 63% [9]. The conclusion of the study was that treatment according to the RADPLAT programme is possible in typical oncology centres in the United States.

# INTENSIFICATION OF RADIOTHERAPY WITHIN THE RADPLAT PROGRAMME

In cases of advanced cancers of the head and neck, intensification of radiotherapy is a recognised means of improving the results of treatment. On this basis, Foote and colleagues [22] undertook to attempt such a boost within the limits of RADPLAT by increasing the rate of irradiation by means of concomitant boost. Initial observations of a group of 19 patients showed that such treatment was unacceptable owing to complications. Among others, the authors reported 2 deaths resulting from sepsis after chemotherapy and 1 case in which amputation of the lower extremities became necessary, owing to thrombosis. The number of chemotherapy cycles was therefore reduced from 4 to 3 for the remainder of the study, though toxicity was not acceptable. From this, it may be deduced that the original RADPLAT programme represents optimal levels of tolerance and side effects and attempts to further intensify the therapy produce no further therapeutic benefits.

#### CONCLUSIONS

To date, the final results of the randomised phase III clinical trials for the assessment of the RADPLAT programme are unknown. Groups which have initially verified the method include Robbins and colleagues [8] of the oncology centre in Memphis and Balma and co-workers in the National Cancer Institute (NKI) of Holland in Amsterdam [20].

The RADPLAT programme represents a particularly interesting proposition for the treatment of advanced cancers of the head and neck in which conventional methods of treatment (surgery and radiotherapy) give highly unsatisfactory results of treatment or simply cannot be applied. The programme is associated with increased logistical problems and significant toxicity, but when viewed in context with the very promising results of treatment, these difficulties are acceptable. However, until the phase III clinical trials are complete there will be a lack of evidence to support this treatment in routine practice.

Our centre in Poznań has completed an initial analysis of results from a pilot study which show complete agreement with the observations of the American and Dutch researchers.

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