# ORIGINAL PAPER

# THE ROLE OF RADIOTHERAPY IN THE TREATMENT OF MALIGNANT MELANOMA.

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## SUMMARY

Malignant Melanoma is recognised by several radiotherapists to be radioresistant. Many radiobiological data and well-known differences in the morphology of melanoma suggest that this claim may be false.
The data obtained are presented in the paper in a historical overview. Principles of the radiotherapy of melanoma are discussed. The results of palliative irradiation of 27 patients, treated at the GreatPoland Cancer Center in the years 1985-1989 are discussed.

## HISTORY

Malignant melanoma has been for many years recognised as a radioresistant tumour basing on a limited number of observations, or lack of regression observed in tumours after conventional treatment (1,8 - 3,0 Gy per day). The rationale for using irradiation technique has been questioned. Special controversy has arisen over the dose per fraction, overall dose and fractionation schedule.
Regardless of doubts and controversies, melanoma was one of the first tumours irradiated (Peschel, 1986; Trott, 1993).

Miescher was among the first authors who printed to differences in the morphology of melanoma and thus to a resulting difference in radiosensivity. He observed higher remissions in tumours that had a higher therapeutic ratio (Miescher,1926). In 1931, Evans and Leucutia described 30 patients treated successfully only with radiotherapy (Evans, 1931). The investigations by Ellis led to a large number of valuable conlusions. He used a total dose of 55 - 60 Gy for 7-10 days. Complete remission was observed in 12 patients in a group of 38 irradiated patients (Ellis, 1939).

Another author who suggested that melanoma is not a radioresistant tumour is Hellriegel. He based his observations on an extensive study made over 25 years (Hellriegel, 1963).
In a group of 95 patients treated only with irradiation he achieved 68% 5-year free-survivals, in the group of 105 patients with a more advanced form of melanoma treated with surgery and irradiation he achieved 62% of 5-year free-survivals.
The daily dose used in the orthovoltage era was 1000 R whereas the total dose was 10000 R for the energy of 30 kV - 50 kV. In the megavoltage era, the most frequently used doses were 50 Gy administered in 20 fractions. This treatment brought in an increase in local and metastatic regression in tumours (Trott, 1993).
Development in radiobiology resulted in a charge in the recognition of melanoma as a radioresistant tumour.

## RADIOBIOLOGICAL CONSIDERATIONS

In 1971 in two papers, similar results concerning the radiobiology of melanoma cells were presented. Barranco et al. published a report which focused on melanoma radiosensivity (Barranco, 1971). The authors proved that the cell survival curve on the skin melanoma cells, shows an atypical wide arm of radioresistency. The value of this discovery was clear for radiobiologists and radiotherapists. The "in vitro" research showed that melanoma cells had a great ability to sublethal damages repairment.
This provided explanation for the melanoma radioresistency during conventional treatment (Meder, 1985). Dewey published similar results obtained from "in vitro" cells (Dewey, 1971). The wide arm of radioresistency was observed when low doses of irradiation were used. He suggested that the use of doses per fraction greater than 4,2 Gy would be more appropriate.

Ellis when using the data obtained by Dewey was able to ascertain the influence of the dose per fraction on the probability of cure (NSD pattern)

for tumours with different radioresistency arms on the survival curves. He claimed that in the case of a high extrapolation number (the ability for sublethal damages repairment), the sterilization effect for the same NSD (similar damages of healthy cells) is larger for a small number of high fractions rather than that for a high number of low fractions. The high extrapolation number is typical for radioresistant tumours. Ellis suggested the use of several high doses for such "radioresistant tumours" (6 Gy or more). His recommendations were accepted by several radiotherapstis who often obtained high percentages of tumour local controls.

Many researches has been done during the last 25 years with often contradictory results (Jenrette, 1996). Thus it was possible to verify Elliss's observations.

Rofstad compared the parameters from the survival curves obtained from melanoma cell lines isolated from xenografts and directly from pathological samples (Rofstad, 1986). He failed to prove the influence of cells origin on the survival curve parameters. In every group of cells he observed a wide range of Do [dose gives an average of one hit per target] (0,57-2,11 Gy) and extrapolation values (1-78). For his analysis he used a linear-quadratic model and an alpha/beta ratio.

The average extrapolation number was 5, but 30% of the values were above 10 or below 3. The average alpha/beta ratio was 7 Gy, 30% of the values were below 3 Gy and 30% of them were above 10 Gy. These results proved the heterogeneity of melanoma cells.

Widel presented the results based on human xenografts characteristics (Widel, 1996). She showed the existence of differences in the dimension of nonoxydatic cells, vascularisation density and reoxygenation level during radiotherapy and also in the ability of sublethal and repairment of lethal damages. These differences can have an influence (apart from radiosensivity) on the heterogeneous response to fractionated radiotherapy. Clinical data showed that the alpha/beta ratio for "in vitro" irradiated cells for different 40 cell lines varied from 0,5 to 63,8 Gy. The radiotherapy of melanoma demands an individualized selection of doses per fraction. Widel suggests a potential usefulness of the study of the "in vitro" melanoma cells radiosensivity for individualisation of the procedure.

The recommended tests for radiosensivity are the following:

- the indirect SF-2 test (survival fraction 2Gy)
- the micronuclear test and
- the fibroblasts differentiation test.

The value of the radiobiological study is limited by the incomplete complementariness of the "in vitro" and "in vivo" cells research. It is well known that a large number (6% to 85%) of cells are hipoxic (Rofstad, 1990; Weischelbaum, 1984). Since the oxygenation of cells is one of the most important factors in cells radiosensivity, it is possible to achieve different results in the same lines of cells in the "in vitro" and " in vivo " conditions.

There are many other factors influencing melanoma cells radiosensivity such as cell damage repairment, phases in the cellular cycle, genetic dependent radiosensivity, hipoxic fraction, ability for reoxygenation and repopulation. All these factors may have a great influence on the radiosensivity.

Weischelbaum et al. suggested that tumours radioresistency may depend on the ability to sublethal damages repairment (UPL) (Weischelbaum, 1984).

The discussion on the protocol is still open. It seems that the "dose - time ratio" and the various values of the alpha/beta ratios can have an important effect on the radiotherapy of melanoma (especially on the changes in doses per fraction) (Wannenmacher, 1986).

## PRINCIPLES OF MELANOMA RADIOTHERAPY

Since the 1970's , high doses have been used in melanoma irradiation (4 - 9 Gy) once or twice a week, with complete remissions and long - time survivals (Adam, 1982; Habermalz, 1976; Hornsey, 1978; Overgaard, 1980; Skowronek, 1997; Strauss, 1981). Surgery is still treatment of choice, therefore, the data available are mainly on palliative irradiation. Patients qualified for radiotherapy have usually tumours in an advanced stage, very often with metastases, and thus not eligible for a comparison with patients who undergo surgery.

This makes it impossible to determinate optimal doses per fraction and total doses for complete remission. In almost all cases, groups of patients are not numerous enough, the localisations of original tumour and metastases are varied, the period of observation is short due to a limited survival length, and the criteria of the response are influenced by the palliation effect rather than by the curing effect.

Habermalz has summarized the results of several studies researches (Habermalz, 1981). In the whole group, 38% (85/221) of complete remissions were obtained after the irradiation of metastases to the skin, subcutaneous tissue and lymph nodes. The percentage of remissions was dependent on the doses per fraction, rather than on the total dose. The differences in the results were especially noticeable in patients with partial remissions : 54% (59/110) in a group irradiated with a dose per fraction lower than 4 Gy, and 83% (92/111) with a dose per fraction higher than 4 Gy.

Different locations of tumours ( the large ones were irradiated more often but with lower doses ), different total doses (a large number of tumours were irradiated with conventional radiation of 20 x 2,5 Gy with inadequate total dose) and short periods of follow-up have some influence on these results.

Overgaard et al. conducted a retrospective research (Overgaard, 1986). They published results of radiotherapy in 100 patients with metastases to skin or lymph nodes. Complete remission was achieved in 49% cases of skin metastases and in 43% cases of lymph node remissions in period of more than 5 years. The complete remission was independent of the total dose, and of the dose per fraction lower than 3 Gy in 38 patients. In these patients, the total dose was also lower when compared with the total doses in the treatment of other cancers. The most important conlusion from Overgaard's research is the definition of melanoma radiosensivity.
Besides, patients who had achieved complete remission had great probability of local control and improvement in their overall survival.

According to Overgaard et al., radiotherapy can be a treatment of choice in patients with melanoma metastases to skin and lymph nodes. Better results can be achieved using radiotherapy combined with hyperthermia.

In one randomized prospective trial (RTOG 83-05) high doses (4x8 Gy for 21 days) were compared with conventional fractionation (20x2,5 Gy for 26 days) (Borgelt, 1980). There was no significant difference in the response to irradiation (60% vs 57%). This is the reason why tolerance to healthy cells should be taken into consideration during radiotherapy. Excessively high doses per fraction are not recommended in the treatment of tumours localised near the tissues with low tolerancy, for example, in the nervous system or parenchymatous organs.

According to Meder, high dose irradiation of localised tumour (without metastases) can be recommended in the case of:
a/ patients not suitable for surgery,
b/ selective patients with melanoma of eyeballs,
c/ postoperative irradiation to local and metastatic tumours,
d/ palliative irradiation for local reccurence, metastases to lymph nodes, single metastases to skin, subcutaneous tissue and internal organs (Meder, 1985).

## THE AUTHORS' OWN RESULTS

In the period between January, 1, 1985 and December, 31, 1989, 27 patients (14 men and 13 woman) with melanoma were irradiated palliatively (aged 22-66) (Skowronek, 1997). All the patients were disqualified from repeated surgery because of tumours inoperability. In all cases, the clinical diagnosis was confirmed on pathological examination. Tumour localisation was as follows: head and neck (7), chest and abdomen (2), back (1), upper extremities (6), lower extremities (11). Patients for irradiation were qualified in the case
of :
- local reccurence : 11 patients
- metastases to regional lymph nodes : 16 patients.

They were irradiated with dose per fraction of 600 cGy, twice a week, to the total dose of 3600 cGy (18 patients) or 4800 cGy (9 patients). The dose of 4800 cGy was given in tumours greater in diameter than 2-3 cm. 9 MV photons were used in 6, Co-60 beam in 15, and 10 MeV electrons in 6 of patients respectively. The energy was selected depending on the localisation and the size of the tumours. Between one and four entry fields were determined. After irradiation, the patients did not receive any another therapy. The follow - up was completed 31 December 1994.

In the group of 27 patients irradiated palliatively, complete remission estimated 4 weeks after the end of the irradiation was obtained in 14 patients, incomplete in 8 and no remission in 5 patients (table I).

| Radiotherapy | Complete remission | Partial remission | No remission |
|---|---|---|---|
| Local reccurence | 7 | 1 | 3 |
| Regional lymph node metastases | 7 | 7 | 2 |
| | 14 (51,9%) | 8 (29,6%) | 5 (18,5%) |

Table I Remission after radiotherapy for various tumours sites

For local recurrences, complete remission was achieved in 63,6% of cases, partial remission in 9,1% and no remission in 27,3%. For metastases to lymph nodes complete remission occured in 50,0% of cases, partial remission in 37,5%, and no response to radiotherapy in 14,3%.

Eleven patients were still alive after 5 years (40,7%), 9 of them (33,3%) without symptoms of the disease. Two patients underwent surgery for consecutive recurrences.

The correlations between the survival and time of diagnosis when compared with choosen prognostic factors, complete remission and radiotherapy causes are shown in table II and III.

| Prognostic factors | Survival rate | | n= |
|---|---|---|---|
| | < 5 years n % | > 5 years n % | |
| **Age :** | | | |
| < 47,2 years | 8 66,7 | 4 33,3 | 12 |
| > 47,2 years | 8 53,3 | 7 46,7 | 15 |
| **Localisation of the primary lesion:** | | | |
| Head and neck | 6 85,7 | 1 14,3 | 7 |
| Chest | 2 | 0 | 2 |
| Back Upper limb | 1 | 0 | 1 |
| Lower limb | 3 50,0 | 3 50,0 | 6 |
| Upper lower | 4 36,4 | 5 63,6 | 11 |
| **Complete remission:** | | | |
| Yes | | | |
| No | 4 28,6 | 10 71,4 | 14 |
| | 12 92,3 | 1 7,7 | 13 |
| | 16/27 59,3 | 11/27 40,7 | 27 |

Table II The 5 - year survival rates and some selected prognostic factors

| Radiotherapy | n = | 5 – year survival rate | mean survival time (month) | |
|---|---|---|---|---|
| | | | from the day of diagnosis | from the start of radiotherapy |
| Local recurrence | 11 | 8/11 (72,7%) | 63,0 | 44,5 |
| Regional lymph node metastasis | 16 | 3/16 (18,8%) | 35,2 | 20,4 |
| | 27 | 11/27 /40,7%/ | | |

Table III The 5-year survival rates for various tumour sites

Among patients irradiated with the total dose of 3600 cGy 8 patients (44,4%), and 3 (33,3%) irradiated with the tocal dose of 4800 cGy survived for 5 years.

A small group of patients did not allow for any statistical analysis.

In our own material, the patients were qualified for radiotherapy in the case of local recurrence on the site of the removed primary tumour or with metastases to regional lymph nodes. High doses per fraction were applied twice a week in accordance with the principles obtained in several oncological centres (Adam, 1982; Habermalz, 1976; Hornsey, 1978; Katz, 1981). No remission was observed only in 5 patients out of 27. Complete remission was seen in 14 patients (46,7%), more often in the cases of local reccurences (63,6%) than in the cases of metastases to lymph nodes (50,0%).

The tendency to differentiate the 5-year survival period was observed in patients irradiated for local reccurence (72,7%), metastases to regional lymph nodes (21,3%) and also in the cases where complete remission was achieved (71,4%) and in progressive disease (28,6%).

The 5-year long survival for 11 patients disqualified from surgery and irradiated palliatively, in spite of the small number of patients in the group, may point to the usefullness of radiotherapy with high doses per fraction for patients with local reccurence after surgery or metastases to regional lymph nodes.

## CONLUSIONS

Nowadays there are no indications to recognise melanoma as a radioresistant tumour. In spite of the developments in radiobiology, there are still a lot of aspects to investigate. The cause for the different radiosensivity of melanoma cells for different doses is probably connected with their heterogeneity. The use of radiosensivity tests, such as the indirect Survival Fraction Test (SF-2), micronuclear test, a fibroblasts differentiation test, may facilitate the individualisation of the dose per fraction protocol.

Radiotherapy is still a method of choice in palliative treatment for inoperable cases, for patients not giving consent to an operation, or for the conservation of limbs. Better therapeutic results will probably be obtained in the future by a combined treatment (radio-, chemio-, immunotherapy and hyperthermia) and by the introduction of irradiation with a high ratio of LPE (Rate, 1988).

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