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CELLULAR RADIOSENSITIVITY AS PREDICTORS OF TREATMENT OUTCOME: WHERE DO WE STAND?

To the Editor: The encouraging results published in the article (1) must be viewed as preliminary and must be confirmed with a larger number of patients and a longer follow-up, as it is clearly stated in the article's conclusion. Responses to the remarks raised by L. Peters *et al.* (2) are as follows:

The cut-off value was determined by testing different percentiles of the alpha distribution (25%, 33%, 50%, 66% and 75%) using a log rank test for all of the 77 patients. The endpoint was locoregional recurrence free survival. The analysis showed that patients in the first percentile (25% lowest alpha values) had a significantly worse LRFS ($p = 0.01$). It also showed that patients in the fifth and last percentile (25% highest alpha values) had a higher LRFS but this was not significant ($p = 0.10$). The alpha value of the upper limit of the first percentile was 0.074 Gy^{-1} and was therefore chosen for the study. In an updated, yet to be published study (median follow-up > 2 years) on a larger number of patients (117), alpha values remained a significant prognostic factor for head and neck and cervical cancers ($p = 0.01$) and for head and neck cancer patients only ($p = 0.04$) (1). These findings tend to suggest that using the CAM plate assay, about 20% of patients can be identified as a high risk group. It is possible that in the near future we will also be able to demonstrate that alpha values might also be useful in identifying about 20% of patients with very radiosensitive tumors.

Since the prognostic value of intrinsic radiosensitivity was tested in this study, we did not think it appropriate to include patients who had palliative or inadequate radiation treatment (geographical misses, overall treatment times that exceeded the conventional treatment times by more than 14 days, and those treated in other centers and for whom technical data could not be retrieved). Moreover, to avoid compounding an already complicated issue, patients who had chemotherapy were excluded from the study. Therefore, we were left with a homogenous group of 56 patients "deemed to have been properly treated". The decision to keep such a small number of patients could have compromised the demonstration of the prognostic significance of alpha values due to the dramatic decline in the number of patients. However, the rationale for maintaining such a small homogenous group proved to be legitimate. It is also obvious that the study of radiosensitivity (and probably also of the pretreatment potential doubling time) should be included in a multivariate analysis. As the number of patients in our study was not very large, we adjusted alpha values on clinical prognostic factors such as the T and N stage and the hemoglobin levels. Alpha values remained a significant prognostic factor when adjusted on T stage ($p = 0.01$) and hemoglobin levels ($p = 0.01$) and were of borderline significance when adjusted on N stage ($p = 0.08$). These findings suggest that alpha values might be an independent prognostic factor.

In conclusion, this study suggests that alpha values are a putative prognostic factor. These positive preliminary findings (as for that of the potential doubling time) should entice us to initiate an international multicentric study which would allow us to perform a multivariate analysis on a sufficient number of patients. This analysis should include, as pointed out by Peters *et al.*, the known clinical prognostic factors and the potential biologic prognostic factors (intrinsic radiosensitivity, pretreatment potential doubling time and possibly the number of tumor clonogens). As time is running out, we should put our shoulders to the wheel and buckle down.

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RADIATION AS ADJUNCTIVE THERAPY TO CYSTECTOMY FOR BLADDER CANCER

To the Editor: The article by Drs. Reisinger, Mohiuddin and Mulholland, that is, a summary of the 10-year experience of a prospective Phase I/II trial of combined pre- and post-operative adjuvant radiation therapy for bladder cancer, is a welcome addition to the literature (1). It includes 78 patients with a median follow-up of 4.3 years. The median follow-up of those patients still surviving is, I suspect, even longer. The acutarial survival at 5 years is given by the pathologic stage of the primary tumor. This is a particularly exact method of staging patients presenting with these tumors but, because of a very significant amount of pathologic up staging (approximately 30% relative to clinical stage) and even some down staging, these results are not able to be compared accurately to the series reporting their results by clinical stage. Nevertheless, the survival rate at 5 years of 67% of all stages is relatively very good as is the 50% survival they report in the 40 patients with high pathologic stage and grade tumors. The pelvic control reported in this series is also good with only 7 of 78 patients developing a pelvic recurrence. This includes only 3 (7.5%) of 40 patients selected for post-operative radiation therapy and only 3 (14%) who were judged to have too superficial a tumor to warrant adjuvant therapy. These good results with regard to pelvic control were seen despite the fact that half the patients underwent only a total cystectomy (no pelvic lymphadenectomy). More than 40% of these patients in this trial died of disseminated disease (patients dying of intercurrent disease were censored). This would imply by retrospective comparison, that preoperative irradiation of 500 cGy does not decrease (prevent) distant metastases. Further it suggests that the excellent local control rate perhaps can be improved on by using combined modality therapy (including systemic multidrug chemotherapy) for higher pathologic stages which would include a lower dose of radiation (this series reports a 30% increase in postoperative complications using 4500 cGy). However, such approaches using systemic chemotherapy *should only be done in the setting of controlled clinical trials* because todate there has been no proven benefit of adjuvant systemic chemotherapy on survival, although two groups using multiple agent chemotherapy have shown a impact on delaying the time in the development of distant metastase (2, 3). If systemic adjuvant chemotherapy is to be used, combinations containing both methotrexate and cisplatin are probably required; if adjunctive radiation is to be combined with chemotherapy, adriamycin is probably best omitted even if the radiation is to be given sequentially (4).

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SHOULD TUMORS BE CLAMPED IN RADIOBIOLOGICAL FRACTIONATION EXPERIMENTS?

To the Editor: The recent article by Dr. Beck-Bornholdt (1) has to be welcomed as an attempt to analyze the extent to which the clamping procedures recommended for experiments on the response of rodent tumors to fractionated irradiation (2) might bias the results of such studies. Dr. Beck-Bornholdt makes a case against irradiating under clamp hypoxia because the surviving stem cells will differ in their spatial distribution, particularly after high doses, from that after ambient irradiation. They will also differ in their pre-irradiation history concerning oxygenation, physiology, and kinetic status. While it is not unreasonable to speculate that the microenvironment to which surviving cells after irradiation of clamped or unclamped tumors are exposed, might affect repair, repopulation and redistribution, there is very little data to prove that this effect plays a significant role during fractionated irradiation with small daily doses, and even little support from experimental protocols. The comprehensive study by Suit *et al.* (3), quoted in Dr. Beck-Bornholdt's paper in a somewhat selective way, rather proves that repair and repopulation are not different between the euoxic cells surviving in clamped tumors and the hypoxic cells surviving in unclamped tumors. For example, the dose equivalent of repair is best determined by comparing single doses and two fractions given in 24 hr: The difference in TCD_{50} is 11.4 Gy in clamped and 11.8 Gy in unclamped tumors. The dose equivalent of repopulation is best determined by comparing schedules giving the same number of fractions in a short time (compatible with complete repair) or with longer intervals. In the five fraction schedule the TCD_{50} increases by 29.4 Gy (clamped) and 28.7 Gy (unclamped), respectively, when the interfraction interval is increased from 1 to 5 days. For the other schedules the conclusions are less clear because, in unclamped tumors, reoxygenation and repopulation affect the TCD_{50} in opposing directions. This is the very reason why clamping is recommended in fractionation experiments of rodent tumors: As insufficient reoxygenation is both an overriding and unpredictable factor of resistance, no interpretation of the results is possible with regard to mechanisms if unclamped tumors are used. The relative importance of reoxygenation, repair, and repopulation therefore remains obscure in the muddle of phenomenological observation, and rational clinical consequences cannot be drawn.

Dr. Beck-Bornholdt makes the claim that some of the fundamental concepts of tumor radiobiology such as "accelerated repopulation during radiotherapy" might be biased because they are based on data obtained from clamped tumors. Yet accelerated repopulation has been first demonstrated in squamous cell carcinomas of patients and only later been confirmed to occur also in squamous cell carcinomas of mice (4), with fractionated irradiation of clamped tumors. In the same series of experiments other tumor types showed no accelerated repopulation although the clamping procedure was identical. This confirms that accelerated repopulation is a genuine response of some types of tumors but not all, during fractionated irradiation. In contrast to its intentions, the discourse of Dr. Beck-Bornholdt provides further arguments for recommending clamping in all radiobiological tumor experiments where time-dependent processes such as repair or repopulation are to be studied and insufficient reoxygenation is an uncontrollable and disturbing factor.

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CLAMPING AND ACCELERATED REPOPULATION IN EXPERIMENTAL TUMORS DURING RADIOTHERAPY: RESPONSE TO DRS. KUMMERMEHR AND TROTT

To the Editor: A few issues need to be clarified w/Drs. Kummermehr's and Trott's letter. In my article (3) I mentioned the results obtained by Suit *et al.* (6) after applying 5, 10, and 20 fractions. Kummermehr and Trott allege that the data were quoted selectively without considering treatments with single doses and two fractions. I do not share their opinion that tumor response to single doses or two large fractions applied within 24 hr is equivalent to tumor response to a continuous fractionated treatment with 10 or more fractions extended over a couple of weeks (2, 4). The results obtained by Suit *et al.* (6) after 10 fractions show that the $TCD_{50\%}$ only increased with increasing overall treatment time when the tumors were clamped during irradiation. This can be interpreted as a notable repopulation, that occurs only in clamped tumors. The results obtained after applying 5 fractions show the same tendency, but not in such a clear manner as was found after 10 fractions.

Kummermehr and Trott claim that interpretation of experimental results is impossible if unclamped tumors are used. At the same time they argue that accelerated repopulation has been first demonstrated in squamous cell carcinomas of patients (7). However, it appears to me that the latter argument should not have been used by the authors, since patients in clinical setting certainly are not treated under clamp hypoxia conditions. Therefore—to put it into the words of Kummermehr and Trott—the "muddle of phenomenological observation" should not allow to derive any interpretation with regard to mechanisms from clinical data.

Yet, the survey by Withers *et al.* (7) on head and neck tumors gained eminent importance in the discussion of accelerated repopulation in tumors during radiotherapy. They presented the results in terms of $TCD_{50\%}$ as a function of treatment time (Fig. 1). The estimated increase in $TCD_{50\%}$ with time, as indicated by the thin lines, is much steeper than the dashed line that describes the rate of increase in $TCD_{50\%}$ as calculated from a 2 month clonogen doubling rate. From their analysis Withers *et al.* (7) suggested that, on average, clonogen repopulation in squamous cell carcinomas of the head an neck accelerates only after a lag period of the order of 4 ± 1 weeks after initiation of radiotherapy. Dubben (5) reanalyzed the same set of data and reported that the increase of $TCD_{50\%}$ with increasing treatment time vanished completely after stratification of the data according to the prescribed dose. This also becomes obvious from Figure 1. The data were stratified into three groups. The low dose group (43–57 Gy; squares) is reasonably fitted by the bold horizontal line at 52 Gy, corresponding to the weighted mean $TCD_{50\%}$ of this group. Also the high dose group (67–76 Gy; circles) is adequately described by the horizontal line at a $TCD_{50\%}$ of 69 Gy, corresponding to the mean $TCD_{50\%}$ of the high dose group. The range of treatment times of the intermediate dose group is too small to detect any correlation to $TCD_{50\%}$. From the stratified analysis it can be concluded that the data are consistent with the idea that treatment duration does *not* affect $TCD_{50\%}$ (5).

Currently, straightforward measurement of repopulation in tumors *during* fractionated radiotherapy is not possible. It can only be determined indirectly by functional endpoints. This implies problems with the interpretation of the results, since the observed effects may be influenced by reoxygenation, recovery or redistribution. If changes observed in tumor response with increasing overall treatment time are exclusively attributed to repopulation, its importance might be overestimated considerably.