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CORRESPONDENCE

Re-irradiation for recurrent head and neck carcinomas (by Dr. Peponi et al)

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In a recent paper Peponi et al. reported the outcomes and toxicity of re-irradiation in patients with recurrent head and neck carcinoma. We fully agree with the conclusion that a new course of re-irradiation may be applicable in cautiously selected patients [1].

Furthermore, Tortochaux et al. showed the results of a randomized phase III trial comparing re-irradiation plus chemotherapy (5FU and hydroxyurea) vs chemotherapy alone (methotrexate) in patients with recurrent or second primary head and neck squamous cell carcinoma in a previously irradiated area [2].

The goal of the study was to evaluate the potential benefit of concurrent re-irradiation plus chemotherapy vs a single chemotherapeutic agent. Premature discontinuation of the trial did not allow drawing firm conclusions. However, there was no suggestion of an improvement in overall survival with re-irradiation compared to chemotherapy alone.

Currently there are no other randomized data with respect to optimal approaches for patients with recurrent head and neck squamous cell carcinoma or second primary in previously irradiated area. In fact, the RTOG started a similar randomized phase III trial, but was closed early due to lack of recruitment. Thus, the evidence to offer re-irradiation as a curative treatment comes mainly from retrospective and phase II trials [3].

In general, for patients with operable disease recurrence surgical resection is considered the standard of care and offers the best chance for long term disease control in 25-45% of the patients [4]. When patients present with unresectable disease or are unable to undergo surgery, the standard treatment is systemic chemotherapy However, chemotherapy alone yields a median survival time of no more than 10 months [4].

There are several important points to make regarding the topic of re-irradiation when considering chemotherapy alone as an alternative. First, re-irradiation induced toxicity is considered high and patients must be carefully selected. However, the selection criteria for re-irradiation remain poorly defined. The practical issues to consider include basic patient characteristics such as performance status, the interval from the initial radiation therapy to recurrence and previously received dose by critical structures. In combination with clinical judgement, these data can be helpful as a framework in decision making [1,3]. Secondly, although the risk of distant metastasis is high, most of these patients will die as a result of uncontrolled tumor growth at the primary site [3,4].

It is also critical to understand that many of the published series used treatment techniques currently considered obsolete.

On the other hand, in recent years the development of IMRT and/or fractionated stereotactic radiation therapy give us new possibilities to offer re-irradiation more safely with a higher local control when compared with those from historical controls [5]. Not only technological aspects, but also re-irradiation with EGFR targeted therapy (cetuximab) should be taken into account. In fact, there is an ongoing phase II trial conducted by GORTEC evaluating re-irradiation with cetuximab (Clinicaltrials.gov Identifier NCT01237483).

Finally, although results are discouraging and the prognosis is poor [1], re-irradiation with or without chemotherapy is the only potentially curative treatment for patients with unresectable disease. New studies are being conducted that may show us encouraging approaches in the near future.

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Reply to Dr. Jon Cacicedo Fernandez de Bobadilla

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We agree with the comments of Dr.Cacicedo. As he has pointed out, reirradiation with or without chemotherapy is considered today the treatment of choice for patients with recurrent head and neck carcinomas [1, 2].

New technologies like IMRT seem to be useful in the treatment of these patients, given that less toxicity may be observed [3,4]. On the other hand, cetuximab combined with radiation therapy can play a critical role in the treatment of patients with locoregionally advanced head and neck cancer [5]. It is important to note that among 19 out of our 35 patients who received cisplatin concomitantly with radiotherapy, there were also 7 patients, who had also received cetuximab. However, no statistically significant difference in locoregional control and overall survival was observed between all these patients and the patients who did not receive any medical treatment. Of course, obviously it is very difficult to extract some definite conclusions because of the small number of patients. This is the reason that we did not consider to publish these data before the accrual of more patients, a procedure that is in progress. So, at this time we published our preliminary results.

We believe that targeted molecular therapy combined with new chemotherapeutic agents in combination with radiation therapy techniques of the new era (IMRT, IGRT) with or without brachytherapy would give better results in patients with recurrent head and neck cancer.

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Significance of the resection margin and risk factors for close or positive resection margin in patients undergoing breast-conserving surgery (by Drs Gatek and Vrana)

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I read with great interest and pleasure the recently published article by Gatek and Vrana “Significance of the resection margin and risk factors for close or positive resection margin in patients undergoing breast-conserving surgery” [1]. The authors have chosen to present one of the most hot issues in breast cancer surgery, as breast conservation surgery is great a challenge, since the multi-disciplinary team needs to balance between the achievement of the optimal aesthetic outcome and radical excision of the cancerous load.

Undoubtedly, one of the crucial questions in breast conservation approaches is if a negative margin can be regarded as adequate clearance. The current data propose different classifications of the risk of recurrence/residual disease, mainly by evaluating the proximity of the cancer cells to the resection margin, as well as the histopathological characteristics of the underlying cancerous lesions. However, the conservative definition of positive/negative margin seems to overlook what appears to be a crucial part of the future of surgical oncology and certainly is nowadays a field of great scientific interest: the local environment surrounding the tumor. Therefore, the complete removal of the cancer cells in the primary site, even with adequately clear resection margins, does not prohibit us to assume that the residual tumor microenvironment might continue to pose a constant risk for local recurrence or even hide elements of residual disease.

More specifically, a disrupted peritumoral microenvironment, for instance with evidence of active inflammation, micro-thrombosis of the vasculature and calcifications, may indicate the existence of a friendly soil for the recurrence of cancer, as cancer cells use the deposited fibrin formations (which are deposited both in the natural course of inflammation and thrombotic events) as scaffolds in order to migrate either locally or to distant metastatic sites [2]. Moreover, there is solid evidence that another common mechanism cancer cells use to escape immunosurveillance and sequentially spread which suggests that cancer cells are attached to activated platelets which form a “cloak” around them, making them inap-

proachable by white blood cells' subtypes that possess anticancerous capabilities [3]. Taking into account that the above mentioned stand as a gross approach to the interactions between the cancer cells, the surrounding tissue and the immune system, our aim is to highlight that surgical oncology will soon face major challenges concerning the misalignment between the objective definition and the oncological impact of the current concept behind the establishment of the term "resection margins".

From this point of view, the examination of the existence of a potentially significant oncological benefit from the complete excision of the disrupted structures surrounding the cancerous lesions, excising beyond the currently regarded as adequately safe resection margins should be the center of future clinical trials. When it comes to breast conservation surgery – and tissue-sparing surgery in general – the radical excision needs to be weighed against the better cosmetic/functional result. However, a potentially new definition of the resection margins, which will address the characteristics of a disrupted surrounding architecture and will result in a more radical surgical approach, shall stratify more accurately the patients who can benefit from breast conservation surgery with a significantly lower risk of residual disease/recurrence.

Once again, I would like to congratulate the authors for their excellent work.

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Reply to Dr. Charalampos Seretis

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We strongly appreciate Dr. Seretis' interest in our work regarding resection margin after breast conserving surgery.

There are no clear recommendations regarding resection margin after breast conserving surgery [1]. The cosmetic outcome due to its psychological impact has a growing importance in recent years, however the malignant basis of the disease may not be forgotten. The multidisciplinary approach for the treatment of early breast cancer has significantly decreased the recurrence rates which could lead to misleading approach that surgery alone is not so important. At the same time the pathologic examination regarding achieving clear resection margin which is highly time and cost consuming should not be forgotten as well. Clear resection margin after the pathologic examination does not necessarily mean that there are no residual tumor cells left postoperatively, which means that clear resection margin doesn't guarantee complete microscopic tumor resection [2,3]. We are focusing on breast cancer surgery for the last 10 years and we are always highlighting multidisciplinary approach to breast cancer treatment. There has to be close cooperation among all specialities involved in the process: radiologist- surgeon- pathologist-medical oncologist and distant recurrences and the excellent cosmetic outcome.

As evidence to the above mentioned approach to breast cancer resection margin we conducted our study where all patients with resection margin less than 5mm underwent re-resection and specimens were evaluated for residual tumor cells. From the presented data is clear that the current recommended resection margin width may not be sufficient and it is questionable if these residual tumor cells will be treated by chemotherapy and radiotherapy. At this moment, after a median follow up of 5 years we are registering and monitoring the recurrence rate in our group of patients which will be compared with the worldwide presented data. Based on a preliminary assessment, the recurrence rate in our group seems to be lower than in studies already published, which may be attributed to our approach to resection margin and also to the close multidisciplinary cooperation among all specialties involved in the treatment of breast cancer in our hospital.

Clear resection margin is the general aim of oncologic surgery, however the relevant definition of resection margin/resection line is not clear [4].

These data are encouraging us to continue our work for improving the care for breast cancer patients.

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