EDITORIAL

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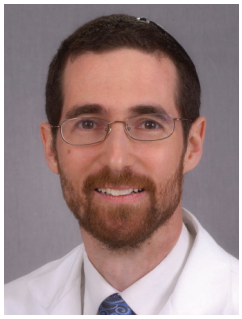
Future ONCOLOGY

Radiation therapy and the immune system: learning to live together



"After many decades of basic research, the importance of the immune response in preventing and treating cancer is no longer controversial."

Yaacov Richard Lawrence[1,2] & Adam P Dicker*[,2]

Dose-response effect in radiation therapy

Today's radiation oncologists were bought up on the concept of 'the more the better', encouraged on by Puck's seductive *in vitro* clonogenic cell survival curves that suggest an exponential relationship between radiation dose and cell kill [1]. Clinicians extrapolated these findings into the clinic, pursuing ever-higher radiation doses in the pursuit of local control, and the sometimes-elusive cancer cure. Clinicians sought to enlarge radiation field size, with the aim of sterilizing at-risk regional lymph-nodes. There is good evidence for the importance of irradiating 'high-risk' lymphoid tissue in Hodgkin's disease and cervical cancer, but the concept has influenced tumor planning in all cancer sites.

A number of key clinical trials from recent decades have contradicted these concepts. Although clearly a minimal dose of radiation is necessary (e.g., 60 Gy in glioblastoma and non-small-cell lung cancer), attempts to escalate doses further have failed to deliver benefit in a range of cancers: esophageal, low-grade glioma, glioblastoma and, most recently, non-small-cell lung cancer [2]. Furthermore, large radiation fields are often poorly tolerated, especially in the context of concomitant chemotherapy. Theodore Puck succeeded in creating cell-survival curves, where more radiation killed more cells, by developing techniques to grow cell monolayers *in vitro*. In doing so he negated systemic effects and the role of the microenvironment [1].

Prostate cancer: field size & radiation dose

In prostate cancer, multiple randomized trails have indeed validated the concept of higher radiation dose achieving better tumor control [3]. However, the utility of larger radiation fields – that is, prophylactic irradiation of the whole pelvis, remains in doubt. A large cooperative group trial (RTOG 9413) enrolled 1323 patients in a two-by-two randomized trial seeking to assess the role of whole-pelvic radiation compared with prostate radiation only; and neoadjuvant hormonal therapy compared with adjuvant therapy. Unfortunately, this trial did not succeed in providing clear answers, possibly owing

KEYWORDS

• combination therapy • immune modulators • ionizing irradiation • radiotherapy • tumor-specific immunity

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[1]Department of Radiation Oncology, Sheba Medical Center, Ramat Gan, Israel
[2]Department of Radiation Oncology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, USA
*Author for correspondence: adam.dicker@jefferson.edu

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"The next generation of radiation oncologists should tailor their treatments and determine dose based not just on tumor-ablative considerations, but also with a view to maximizing the anti-tumor immune response."

to an unexpected interaction between the size of the radiation field and hormonal therapy [4]. The currently accruing trial RTOG 0924 is trying to answer the question regarding field size.

The manuscript published in this issue by Pinkawa *et al.* provides important insight regarding why whole pelvic irradiation may be less beneficial than expected in prostate cancer [17]. Pinkawa *et al.* retrospectively reviewed hematological changes during radiation therapy for prostate cancer. They noted that: radiation therapy significant depressed all blood lineages in peripheral blood, especially lymphocytes; these changes were prolonged – continuing at least 6–7 weeks following completion of therapy (unfortunately, we do not know what happens at later time points); whole-pelvic radiation therapy is more detrimental than prostate-only radiation therapy; and neoadjuvant hormonal therapy decreased hemoglobin levels. Although end points in this study were confined to crude blood counts, we speculate that they reflect a detrimental impact on immune system function and tumor oxygenation, possibly explaining the disappointing results of RTOG 9413.

Role of the immune system in cancer therapy

After many decades of basic research, the importance of the immune response in preventing and treating cancer is no longer controversial. For many years, we have known that subjects with prolonged immunosuppression are at increased risk of developing cancers [5–7]. More recently Phase III randomized trials have demonstrated the efficacy of immunotherapy in metastatic melanoma, renal cell cancer and prostate cancer, with trails underway in almost every disease site.

• Radiation therapy & the immune system

The relationship between radiation therapy and the immune system is complex [8,9]. On the one hand, radiation therapy may augment the immune response, for example, by killing cancer cells, increasing the tumor's antigenicity; and rendering surviving tumor cells more susceptible to immune-mediated killing through increased MHC class I presentation. On the other hand, the immune system may help radiation therapy, eradicating residual disease inside and outside of the radiation field **(Figure 1)**. The extreme demonstration of these interactions is the occasionally observed phenomenon when radiation can also reduce tumor growth outside the treatment field, the so called 'abscopal effect'.

More recently, a research team at John Hopkins led by Stuart Grossman has suggested another mechanism through which radiation may suppress the immune response [10]. They noted that in a range of cancers (high-grade glioma, squamous head and neck cancer, pancreatic adenocarcinoma – both in the locally advanced and adjuvant setting, non-small-cell lung cancer) radiation/chemoradiation can

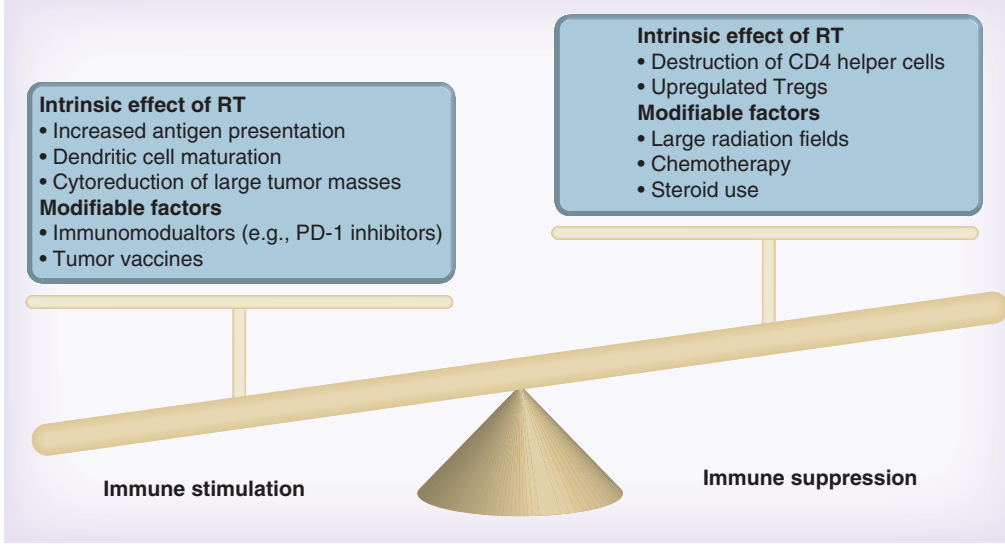

Figure 1. Balance between radiation-induced stimulation and suppression of the immune system.
RT: Radiation therapy.

induce severe treatment-related lymphopenia. Furthermore, they correlated severe lymphopenia with early tumor progression in each of these disease settings [10–14].

It is often assumed that the effect of radiation therapy on peripheral blood counts is the result of bone marrow irradiation, where the normal stem cells are very sensitive to DNA damage. Two recent papers propose alternative mechanisms: lymphopenia maybe caused by apoptosis of lymphocytes passing through the radiation field [14]. The authors estimate that during 6 weeks of partial brain irradiation in glioblastoma, 99% of lymphocytes receive at least 0.5 Gy, with a mean circulating lymphocyte dose of 2 Gy sufficient to induce apoptosis in these highly sensitive cells. A complimentary paper suggests that cytokine deficiency may be an aggravating factor. Glioblastoma patients with lymphopenia were unable to mount an appropriate compensatory cytokine response (IL-7 and Il-15) that would normally act to increase the circulating lymphocyte population [15].

Looking only at crude blood counts may underestimate the effect of cytotoxic therapies on the immune system. Schuler *et al.* examined lymphocyte subtypes in patients with head and neck cancer undergoing chemoradiation [16]. They found that chemoradiation decreased the overall number of circulating CD4 helper cells, but paradoxically increased the number of $CD4^+$ $CD39^+$ Tregs that serve to dampen the immune response. Furthermore they found that the increase in Tregs persisted years after the conclusion of therapy.

Modulating the immune system–radiation interaction

For many years, we have downregulated the immune system by prescribing chemotherapy and steroids during radiation therapy. The expanding arsenal of immunomodulators (PD-1 inhibitors, tumor vaccines and adoptive cell transfer therapies) provides us with unprecedented opportunities to modulate and activate the immune system during radiation therapy. The challenges are immense, and investigators will need to choose the most appropriate patients, immunomodulators and radiation therapies in order to succeed.

Pinkawa *et al.*'s paper, informs us that despite the efficacy of radiation therapy in prostate cancer, its use is associated with relative lymphopenia, and likely immunosuppresion [17]. Either we should avoid large radiation fields, or find ways to counter the radiation-induced lymphopenia. The next generation of radiation oncologists should tailor their treatments and determine dose based not just on tumor-ablative considerations, but also with a view to maximizing the anti-tumor immune response.

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References

1 Puck TT, Marcus PI. Action of x-rays on mammalian cells. *J. Exp. Med.* 103(5), 653–666 (1956).

2 Bradley JD, Paulus R, Komaki R *et al.* A randomized Phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/- cetuximab for stage IIIA/IIIB non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617. Presented at: *53rd ASTRO Annual Meeting.* FL, USA, 2–6 October 2011.

3 Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. *Radiother. Oncol.* doi:10.1016/j.radonc.2013.09.026 (2013) (Epub ahead of print).

4 Roach M 3rd, Desilvio M, Lawton C *et al.* Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J. Clin. Oncol.* 21(10), 1904–1911 (2003).

5 Kaplan HS. Role of immunologic disturbance in human oncogenesis: some facts and fancies. *Br. J. Cancer* 25(4), 620–634 (1971).

6 Penn I. Malignancies associated with renal transplantation. *Urology* 10(1 Suppl.), 57–63 (1977).

7 Allison AC. Tumour development following immunosuppression. *Proc. R. Soc. Med.* 63(10), 1077–1080 (1970).

8 Hodge JW, Guha C, Neefjes J, Gulley JL. Synergizing radiation therapy and immunotherapy for curing incurable cancers. Opportunities and challenges. *Oncology* 22(9), 1064–1070; discussion 1075, 1080–1081, 1084 (2008).

9 Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J. Natl Cancer Inst.* 105(4), 256–265 (2013).

10 Balmanoukian A, Ye X, Herman J, Laheru D, Grossman SA. The association between treatment-related lymphopenia and survival in newly diagnosed patients with resected adenocarcinoma of the pancreas. *Cancer Invest.* 30(8), 571–576 (2012).

11 Campian J, Sarai G, Ye X, Marur S, Grossman SA. The association between

severe treatment-related lymphopenia and progression free survival in patients with newly diagnosed squamous cell head and neck cancer. *Head Neck* doi:10.1002/hed.23535 (2013) (Epub ahead of print).

12 Campian JL, Ye X, Brock M, Grossman SA. Treatment-related lymphopenia in patients with stage III non-small-cell lung cancer. *Cancer Invest.* 31(3), 183–188 (2013).

13 Wild AT, Ye X, Ellsworth SG *et al.* The association between chemoradiation-related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. *Am. J. Clin. Oncol.* doi:10.1097/COC.0b013e3182940ff9 (2013) (Epub ahead of print).

14 Yovino S, Grossman SA. Severity, etiology and possible consequences of treatment-related lymphopenia in patients with newly diagnosed high-grade gliomas. *CNS Oncol.* 1(2), 149–154 (2012).

15 Ellsworth SG, Balmanoukian A, Kos F *et al.* Sustained CD4-driven lymphopenia without a compensatory IL-7/IL-15 response among patients treated with radiation therapy and temozolomide for high-grade glioma. *OncoImmunology* 3, e27357 (2014).

16 Schuler PJ, Harasymczuk M, Schilling B *et al.* Effects of adjuvant chemoradiotherapy on the frequency and function of regulatory T cells in patients with head and neck cancer. *Clin. Cancer Res.* 19(23), 6585–6596 (2013).

17 Pinkawa M, Djukic V, Klotz J *et al.* Hematologic changes during prostate cancer radiation therapy are dependent on the treatment volume. *Future Oncol.* 10(5), 835–843 (2014).