

## AAPM Refresher Course Syllabus

### **Introduction to Extracranial Stereotactic Radiosurgery:**

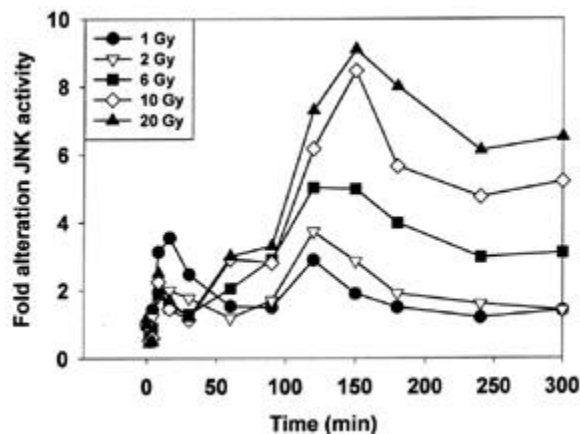
### **III. Radiobiological Considerations and Future Directions**

Brian D. Kavanagh, MD, MPH  
Associate Professor and Vice-Chair  
Department of Radiation Oncology  
University of Colorado Comprehensive Cancer Center  
Anschutz Cancer Pavilion  
1665 N. Ursula St., Box F706,  
Aurora, Colorado 80010-0510  
Phone: 720-848-0116, Fax: 720-848-0222  
Email: [Brian.Kavanagh@UCHSC.edu](mailto:Brian.Kavanagh@UCHSC.edu)

Principles and problems of both classical radiobiology and modern molecular radiobiology can be viewed from a fresh perspective in relation to Extracranial Stereotactic Radiosurgery, herein considered in the broader context of Extracranial Stereotactic Radiation Therapy (ESRT). ESRT opens up a broad range of new opportunities for clinical and related translational investigations across. Selected major topics of established or potential relevance to ESRT are presented here in the hope of piquing interest and provoking ideas.

### *Molecular Radiobiology and Radiogenetic Therapy*

Ionizing radiation is among the many agents capable of triggering cascades of molecular signaling events inside mammalian cells [Dent, 2003]. The pathways involved can involve complex interactions including both a primary phase directly activated by radiation and a secondary phase mediated by soluble factors synthesized in response to the radiation. Especially for the latter condition, there is evidence to suggest a dose-response effect that extends through the range of doses clinically applied in ESRT. For example, Dent and colleagues demonstrated that the c-Jun NH<sub>2</sub>-terminal kinase (JNK) pathway activated by ionizing radiation in a biphasic pattern, the second phase of which appears to be radiation dose-dependent at least up to 20 Gy (figure 1) [Dent, 1999].



**Figure 1.** Dose-dependence of radiation-induced secondary activation of JNK [modified from Dent, 1999].

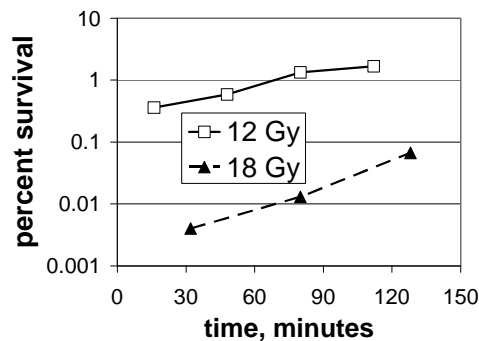
One possible application of radiation to control an intracellular process is in the realm of gene therapy. The term “radiogenetic therapy” was coined to refer to the clinical administration of radiation for the purpose of selectively inducing gene expression, typically in a setting where viral vectors have been introduced to carry the gene into the tumor [Advani, 1997]. The Egr-1 gene is activated by radiation and can be linked to a DNA sequence that encodes tumor necrosis factor (TNF) alpha, a radiosensitizing cytokine [Weichselbaum, 1994; Hallahan, 1995]. TNFerade, an adenoviral vector carrying the transgene encoding for human TNF-alpha linked to the radiation-inducible EGR-1 promoter, has been successfully evaluated in Phase I trial in human patients with pancreas cancer and soft tissue sarcomas receiving conventionally fractionated external beam radiotherapy [Hanna, 2003; Vijayakumar, 2003]. Radiogenetic therapy has not yet

been applied in concert with ESRT, but there could be potential spatial and dosimetric advantages for such a combination, in cancer therapy and perhaps even in other settings, if radiation-inducible promoters were linked to genes encoding for proteins of therapeutic benefit in non-malignant disease.

### *The dose rate problem*

Less future vision, more present-day practical problem is the issue of the intra-fraction radiation dose delivery rate. Routinely ignored entirely in clinical radiotherapy administration, the rate at which tumor cells are exposed to radiation within a single treatment can have a profound impact on the expected cytotoxicity of the radiation. The problem is relevant to single fraction cranial radiosurgery [Benedict, 1997], high dose rate brachytherapy [Arnfield, 2002], and intensity-modulated radiotherapy [Welsh, 2003]. Given that ESRT generally involves technically complex patient setups and often multiple treatment fields, with individual treatments lasting considerably longer than conventional fractions of radiation, it is expected that the dose rate problem is a potential problem for ESRT, also.

The detrimental effect of lengthy treatment times in linear accelerator-based stereotactic radiosurgery was well demonstrated experimentally by Benedict and colleagues [Benedict, 1997]. U-87MG human glioma cells were irradiated with 6 MV X-rays to doses ranging from 6 to 18 Gy over a range of total irradiation times representing the range of what is sometimes required for multiple-isocenter, multiple-arc treatment delivery. The cell survival increased with increasing total irradiation time, presumably a consequence of cellular repair mechanisms that would compromise the efficacy of treatment if the duration of an individual fraction is excessively prolonged (figure 2).



**Figure 2.** Percent survival of U-87MG cells following exposures of 12 or 18 Gy, delivered over the duration of time on the x-axis. Note that for the 18 Gy dose level, increasing the length of treatment from approximately ½ hour to 2 hours corresponds to an order of magnitude decrement in cytotoxicity [redrawn from Benedict, 1997].

Arnfield and colleagues evaluated a situation that can occur commonly during a high-dose-rate (HDR) brachytherapy treatment. Because the distance between a point within a tumor and the radioactive source can vary considerably as the source moves through the planned sequence of dwell positions, the dose rate at that point may vary by a factor of 100 or more. It was hypothesized that the sequence of dose delivery might affect the radiobiological effect. Tumor cell survival was assayed in two conditions of dose rate sequence: initial exposure at a true, HDR-caliber high exposure rate (240 Gy/hr) prior to exposure at an intermediate dose rate (3.5 Gy/h), or vice versa. The results indicated that when the intermediate-dose-rate component was given before the HDR component, there was increased tumor cell survival even if the same nominal total dose was given. This effect was suspected to result from either induced radioresistance or sublethal damage repair [Arnfield, 2002]. Interestingly, when Welsh and colleagues calculated the average dose-rates for IMRT treatment, it was observed that since the average time required to treat patients using IMRT was 25 minutes (range 12-35 min), corresponding to an average dose-rate of 7.2 cGy/min. These dose-rates were much lower than conventional treatment rates of 30-300 cGy min, raising concern about possible adverse effect on the treatment efficacy [Welsh, 2003].

*Dose inhomogeneity and the influence of resistant subpopulations*

Because ESRT involves the administration of tightly constructed dose distributions targeting discrete tumor nodules in a shortened, hypofractionated course of treatment, the relationship between radiation dose and tumoricidal effect may be studied without the same potential concerns regarding tumor cell repopulation that apply during conventionally fractionated external beam radiotherapy. However, variations in ESRT delivery techniques between institutions and interpatient variability within institutions can render it difficult to interpret the true dose-response relationship and, additionally, are a potential impediment to the development of multi-institutional clinical trials. Kavanagh and colleagues addressed this problem by comparing the relative merits of two commonly used indices that describe the composite biological effectiveness of a complex dose distribution: equivalent uniform dose (EUD) and tumor control probability (TCP). The EUD was calculated as follows:

$$EUD = 2Gy \frac{V \ln \left[ \frac{1}{V} \sum_{i=1}^N V_i (SF_2)^{\frac{D_i}{2Gy}} \right]}{\ln(SF_2)}$$

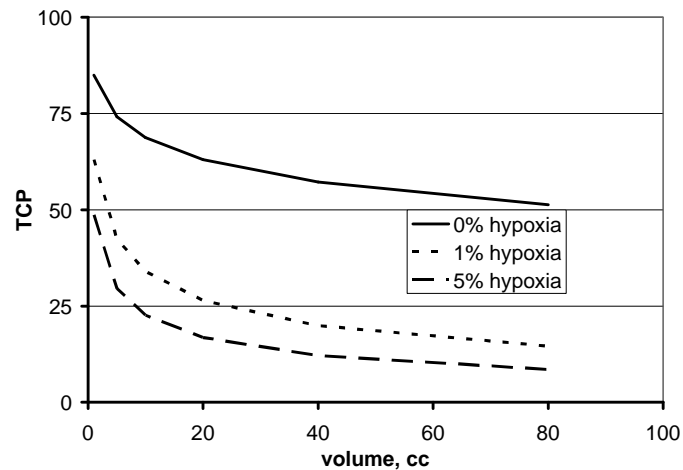
where  $V$  is total volume,  $V_i$  is the volume of the  $i$ th sub-volume within the dose-volume histogram (DVH),  $D_i$  is the dose to the  $i$ th subvolume, and  $SF_2$  is the surviving fraction after 2 Gy. TCP was calculated according to the following formulas:

$$TCP = \prod BCP_j$$

$$BCP = \exp(-N \times SF)$$

where  $BCP$  is the bin control probability of a subpopulation of cells,  $N$  is the number of cells in the bin,  $SF$  is the surviving fraction after the dose given, and  $BCP_j$  is the  $j$ th bin considered. It was observed that the EUD, less sensitive to estimates of cell surviving fraction and number of tumor clonogens, appears more robust for the prospective description of ESR, while TCP is likely more valuable for a *post hoc* estimation of radiosensitivity parameters [Kavanagh, 2003].

Kavanagh and colleagues additionally considered a special problem that complicates ESRT, namely the presence of a subpopulation of tumor cells of significantly altered radiosensitivity. The surviving fraction of hypoxic cells, for instance, is likely to be at least 10 times higher than that of well oxygenated tumor cells after ESRT-range doses. The combined influence of tumor volume and percent hypoxic cells upon TCP estimates, perhaps surprisingly strong, is illustrated in figure 3. Even a very low percentage of hypoxic cells will likely reduce the probability of tumor control substantially.



**Figure 3.** Tumor volume versus TCP after ESRT involving 3 fractions of 15 Gy. The hypoxic fraction varies as indicated, and the hypoxic cell  $SF_{15}$  was estimated to be 10 times greater than the  $SF_{15}$  in well oxygenated conditions. The latter  $SF_{15}$ , for well oxygenated conditions, was estimated from published reports [from Kavanagh, 2003].

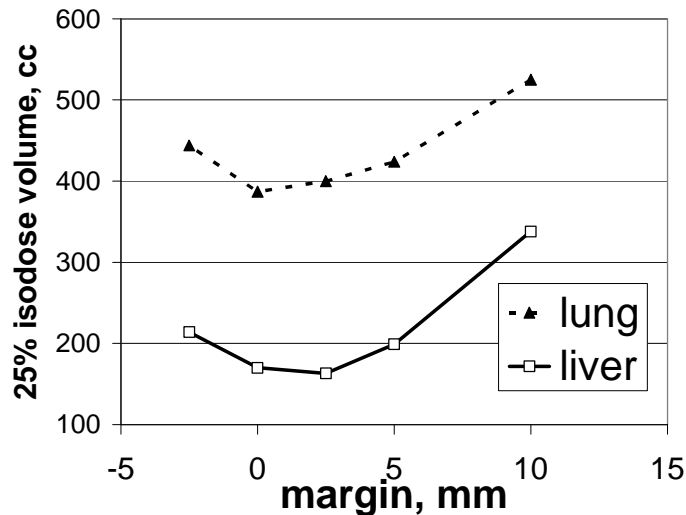
Careful longitudinal observations of tumor control and normal tissue complications following ESRT can yield insight into true *in vivo* radiosensitivity parameters, as long as the influence of dose homogeneity within the target volume is appropriately reconciled. Once the safety and maximally tolerated dose of ESRT has been established for a particular clinical application, avenues for future investigations of ESR could include the combination of ESR with a radiosensitizer, for instance an enhancer of oxygen delivery such as RSR13, to exploit the typical fraction size dependence of radiosensitization via oxygen delivery enhancement or other chemical modification.

*The physics-clinical-biology interface: target margin determination*

In one of the first descriptions of ESRT methodology, Lax and colleagues describe the use of multiple static beams with apertures smaller than the target when considered from a “beam’s eye view” perspective” [Lax, 1994]. They argue that this method can achieve a higher dose centrally within the tumor with only modest increases in the dose within the volume of normal tissue just outside the tumor.

In a more quantitative assessment of the potential biological impact of margin selection upon both tumor and normal tissue dose, Cardinale and colleagues analyzed the impact of varying the margin around the planning target volume (PTV) for a lung and liver ESRT case [Cardinale, 1999]. For each of the two targets, plans were generated with block margins of -2.5 to 10 mm around the PTV. All plans were normalized such that 99% of the PTV was covered by the prescription isodose volume. The following indices were calculated for each plan: (1) maximum dose divided by prescription dose (MDPD); (2) the volume of the prescription isodose surface divided by the PTV volume (PITV); (3) the volume of non-PTV tissue contained in the 100, 90, 80, 50, and 25% of prescription isodose volumes; and (4) the Normal tissue complication probabilities (NTCP) based upon the Lyman model parameters.

As it would have been expected, Cardinale and colleagues noted that with increasing margin, the MDPD decreases while the PITV increases. There were notable differences, however, in the volume of non-PTV normal tissue covered as margin varied (figure 4)



**Figure 4.** Block margin around PTV versus volume of non-PTV normal tissue for multiple field ESRT to a lung and liver tumor [drawn from Cardinale, 1999].

Although Cardinale and colleagues also analyzed NTCP predictions, it can be argued that for parallel organs such as liver and lung, mean dose might be a better prediction of functional compromise. This issue will be addressed further during the presentation, with additional examples of the effects of margin variation on EUD, TCP, and mean normal tissue dose.

### *Ongoing Clinical trials*

There are several single institution, multi-institutional, and cooperative group trials currently open in the United States and Europe. First, the RTOG will be coordinating a protocol entitled “A Phase II Trial of Extracranial Stereotactic Radioablation in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer”, slated to open in the latter part of 2003 [personal communication, RD Timmerman, PI]. Eligible patients will have histologically confirmed non-small cell cancer of the lung, clinically staged T1-T3N0M0. T2 and T3 primaries must be  $\leq 7$  cm in maximum diameter, and only T3 tumors defined by chest wall invasion alone are included. The primary tumor must be deemed technically resectable; however, the patient should have underlying medical problems that would prohibit tolerance of the resection, a status deemed “medically inoperable.”

ESRT dosimetry specifications are detailed in the protocol. Briefly, the gross tumor volume (GTV) will include the primary tumor alone. An additional 0.5 cm in the axial plane and 1.0 cm in the longitudinal plane (cranio-caudal) will be added to the GTV to constitute the planning treatment volume (PTV). Multiple field beam arrangements, planar or non-coplanar, will be used to administer 3 fractions of 20 Gy to the PTV. The primary endpoints is to determine if radiotherapy involving high biological dose with limited treatment volume (using ESR techniques) achieves acceptable local control (i.e.,  $\geq 80\%$ ) while maintaining an acceptable toxicity profile with larger patient numbers in frail patients with early stage non-small cell lung cancer.

At the University of Colorado and Indiana University, there is an open trial of ESRT for hepatic tumors, “Multi-institution Phase I/II Dose Escalation Study of Extracranial Stereotactic Hypofractionated Radioablation for Liver Metastases [T Schefter, H Cardens, PIs]. Originally, the protocol included also patients with primary hepatocellular carcinoma, but there are now two separate protocols to address these 2 clinically distinct conditions. Other institutions will also begin participating soon. Eligibility criteria include a maximum tumor diameter  $\leq 6$  cm, 3 or fewer discrete liver lesions = 3; and known diagnosis of metastatic solid tumor present in the liver. The trial is a dose escalation study; the first cohort received 3 fractions of 12 Gy to the PTV. Additional dose escalation will be accomplished until a DLT is reached; an extended phase II study will then be conducted at the maximum tolerated dose.

The German Cancer Research Center is sponsoring a phase III study of ESRT for the treatment of liver metastases; patients will be randomized between a schedule of 3 fractions of 12.5 Gy or a single 26 Gy fraction. A phase I study of single fraction extracranial stereotactic radiosurgery is ongoing at Wake Forest University [V Stieber, personal communication], and at the Medical College of Virginia is an ongoing “Phase II Study of Fractionated Stereotactic Body Radiosurgery in Patients With Liver Metastases, Lung Metastases, or Other Advanced Tumors in Radiosensitive Organs” [D Song, PI].

## REFERENCES

- Advani SJ, Chmura SJ, Weichselbaum RR. Radiogenetic therapy: on the interaction of viral therapy and ionizing radiation for improving local control of tumors. *Semin Oncol*. 1997 Dec;24(6):633-8.
- Arnfield MR, Lin PS, Manning MA, Arthur DW, Kavanagh BD, et al. The effect of high-dose-rate brachytherapy dwell sequence on cell survival. *Int J Radiat Oncol Biol Phys*. 2002 Mar 1;52(3):850-7.
- Benedict SH, Lin PS, Zwicker RD, et al. The biological effectiveness of intermittent irradiation as a function of overall treatment time: development of correction factors for linac-based stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys*. 37(4):765-9, 1997.
- Cardinale RM, Wu Q, Benedict SH, Kavanagh BD, et al. Determining the optimal block margin on the planning target volume for extracranial stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys*. 1999 Sep 1;45(2):515-20.
- Dent P, Yacoub A, Contessa J, et al. Stress and radiation-induced activation of multiple intracellular signaling pathways. *Radiat Res*. 2003 Mar;159(3):283-300.
- Dent P, Reardon DB, Park JS, et al. Radiation-induced release of transforming growth factor alpha activates the epidermal growth factor receptor and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death. *Mol Biol Cell*. 1999 Aug;10(8):2493-506.
- Hallahan DE, Mauceri HJ, Seung LP, et al. Spatial and temporal control of gene therapy using ionizing radiation. *Nat Med*. 1995 Aug;1(8):786-91
- Hanna N, Chung T, Hecht JR et al. TNFerade in pancreatic cancer. The results of the run-in phase of a major randomized study in patients with locally advanced pancreatic cancer. ASCO Proceedings, 2003.
- Kavanagh BD, Timmerman RD, Benedict SH, et al. How should we describe the radiobiologic effect of extracranial stereotactic radiosurgery: Equivalent uniform dose or tumor control probability? *Med Phys*. 2003 Mar;30(3):321-4.
- Lax I, Blomgren H, Naslund I, Svanstrom R. Stereotactic radiotherapy of malignancies of the abdomen. *Acta Oncol* 1994;6:677- 683.
- Vijayakumar S, Mundt AJ, Nemunaitis J, et al. TNFerade, an adenovector encoding the human tumor necrosis factor alpha gene, in soft tissue sarcoma. A Phase I study. ASCO Proceedings, 2003.
- Weichselbaum RR, Hallahan DE, Beckett MA, et al. Gene therapy targeted by radiation preferentially radiosensitizes tumor cells. *Cancer Res*. 1994 Aug 15;54(16):4266-9.
- Welsh JS, Burkhamer M, Fowler J, et al. Radiation Dose-Rate Considerations with Intensity Modulated Radiation Therapy. ESTRO, 2003.