Radiation enhancement of metastasis: a review

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(Received 10 October 1990; accepted 29 October 1990)

Virtually every modality employed in the treatment of cancer has demonstrated an adverse effect upon metastasis under some conditions. This review surveys the experimental and clinical literature pertaining to the untoward effects of ionizing radiation upon metastatic processes. Two processes are described: (1) enhancement of metastases following local tumor irradiation; (2) localization of metastasis in previously irradiated normal tissues. In the first process the experimental evidence indicates a local effect of irradiation upon the tumor–stroma interface. It predominates under conditions of non-curative radiation doses. There is no proof that this process occurs in clinical practice, but a review of data provides suggestive evidence for its existence following non-curative therapy. The second process is documented both experimentally and clinically. It requires the presence of viable, circulating tumor cells and appears mediated through vascular damage. The few clinical reports suggest that this effect is rare in practice. The clinical significance of both processes appears small under conditions of effective tumor therapy, but it is speculated that inadequate tumor irradiation, or irradiation of normal tissues with uncontrolled tumor elsewhere, may be deleterious.

Introduction

The goal of cancer treatment is to reduce or eliminate the primary tumor and its metastases. Many investigators, however, have noted untoward perturbations of metastasis following treatment under certain experimental or clinical conditions. Perhaps of greatest concern are the observations of enhancement of the rate of metastasis above that seen or expected when other treatments or no treatment was applied.

Modalities in which metastasis enhancement has been noted include the current principal forms of treatment: surgery, radiation therapy, chemotherapy, as well as a number of other agents (table 1).

One modality, herein reviewed, is ionizing radiation. The first major experimental study investigating the effect of local tumor irradiation in metastasis frequency was reported by H. S. Kaplan and Edwin D. Murphy in 1949 [62]. In 1961 Thomas L. Dao and George Moore extended prior clinical observations on the apparent preferential localization of metastasis in heavily irradiated normal tissues [25]. The findings of these two salient studies were followed by many investigations and the data were reviewed in 1978 and 1984 respectively [86, 52]. Because of further important evidence, it seems useful to examine the cumulative clinical and laboratory experience in order to seek to clarify the occurrence and mechanisms, and their clinical significance, and to give suggestions for further experiments and clinical observations.

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Table 1. Agents other than irradiation associated with alterations of metastatic patterns in experimental tumor systems.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Increased</th>
<th>Decreased or no effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical or other trauma</td>
<td>2, 5, 21, 37, 57, 108, 109</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>17–19, 75, 86, 87, 93, 99, 125</td>
<td>138</td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>8, 29, 154, 162</td>
<td>9, 44, 49</td>
</tr>
<tr>
<td>Hypoxic cell radiosensitizers</td>
<td>61, 79, 82, 110</td>
<td>6</td>
</tr>
<tr>
<td>Steroids</td>
<td>5, 11, 81</td>
<td></td>
</tr>
<tr>
<td>Stress (of immobilization)</td>
<td>4, 7</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>41, 121</td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Hypervitaminosis A</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Interferon</td>
<td>70, 103</td>
<td></td>
</tr>
<tr>
<td>Ultraviolet rays</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Lineolic acid</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium granulolosum extract</td>
<td></td>
<td>83</td>
</tr>
</tbody>
</table>

†This list is not exhaustive, but is intended to represent examples of the variety of agents that appear to affect metastasis, sometimes in opposite ways under different conditions.

Two apparently distinct effects have been described:

1. The increase of metastasis following local tumor irradiation.
2. The increased localization of metastases in previously irradiated normal tissues.

These will be reviewed in the following two sections.

Effect of local tumor irradiation on metastatic behavior

Experimental studies

As seen in table 2 a wide variety of experimental conditions were utilized in experiments involving local tumor irradiation and subsequent observation of the rate of metastasis. The principal control animals were generally not sham-irradiated. The doses were generally single fractions and the tumors, transplanted, of varying degrees of immunogenicity in host populations representing a range of genetic inhomogeneity. Exceptions to the above conditions are noted in the table.

The early studies by Krebs [68] and Yamamoto [161] were suggestive but inconclusive for metastasis enhancement by irradiation. Following the definitive experiments of Kaplan and Murphy [62], a series of investigations confirmed that the rate of pulmonary metastasis was increased following single tumor exposures between 800 and 3000 cGy. von Essen and Kaplan [151], concerned that local irradiation might effect longevity and thus permit more metastases to develop, equilized survival in both experimental and sham-irradiated control groups. A significant increase of pulmonary metastases was found in the irradiated group. Kaae [59] analyzed the frequency of metastasis at different survival times for control and
Table 2. Effects of local tumor irradiation on metastatic behavior in experimental systems.

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Ref.</th>
<th>Host</th>
<th>Tumor*</th>
<th>Dose in cGy b</th>
<th>Effect of radiation compared to non-irradiated control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1929</td>
<td>Krebs</td>
<td>68</td>
<td>Mouse</td>
<td>Sarcoma</td>
<td>?</td>
<td>Slight increase of lung metastases. Inconclusive data.</td>
</tr>
<tr>
<td>1936</td>
<td>Yamamoto</td>
<td>161</td>
<td>Rabbit</td>
<td>Sarcoma</td>
<td>?</td>
<td>Increased bone metastases. Inconclusive data.</td>
</tr>
<tr>
<td>1949</td>
<td>Kaplan and Murphy</td>
<td>62</td>
<td>Mouse</td>
<td>Mammary carcinoma</td>
<td>400–1000</td>
<td>Four-fold increase of pulmonary metastases.</td>
</tr>
<tr>
<td>1952</td>
<td>von Essen and Kaplan</td>
<td>151</td>
<td>Mouse</td>
<td>Mammary carcinoma</td>
<td>800–3000</td>
<td>Confirmed above. No effect following irradiation of host alone or tumor alone.</td>
</tr>
<tr>
<td>1953</td>
<td>Kaae</td>
<td>59</td>
<td>Mouse</td>
<td>Mammary carcinoma (spontaneous)</td>
<td>2000</td>
<td>Four-fold increase of pulmonary metastase.</td>
</tr>
<tr>
<td>1959a</td>
<td>Olch et al.</td>
<td>91</td>
<td>Mouse</td>
<td>Melanoma</td>
<td>3000</td>
<td>Reduced numbers of pulmonary metastases in majority, increased numbers in remaining.</td>
</tr>
<tr>
<td>1959b</td>
<td>Olch et al.</td>
<td>92</td>
<td>Mouse</td>
<td>Mammary carcinoma melanoma</td>
<td>2000–2750</td>
<td>Incidence of metastasis similar, although increased number of metastases in irradiated groups.</td>
</tr>
<tr>
<td>1960</td>
<td>Sikov et al.</td>
<td>123</td>
<td>Mouse</td>
<td>Lymphosarcoma</td>
<td>800</td>
<td>No changes in metastatic frequency. Tumor bearing legs amputated 10 days p.rad.</td>
</tr>
<tr>
<td>1970</td>
<td>Suit et al.</td>
<td>129</td>
<td>Mouse</td>
<td>Mammary carcinoma</td>
<td>6000–6400</td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>van den Brenk and Sharpington</td>
<td>146</td>
<td>Rat</td>
<td>Sarcoma</td>
<td>100–6000</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Ref.</td>
<td>Host</td>
<td>Tumor</td>
<td>Dose in cGy</td>
<td>Effect of radiation compared to non-irradiated control</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>------</td>
<td>------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>1971</td>
<td>Crile and Deodhar</td>
<td>21</td>
<td>Mouse</td>
<td>Carcinoma</td>
<td>4000</td>
<td>Decreased metastases in cured animals.</td>
</tr>
<tr>
<td>1972</td>
<td>van den Brenk et al.</td>
<td>145</td>
<td>Rat</td>
<td>Sarcoma</td>
<td>750–4000</td>
<td>Suggestive growth stimulation of metastases with 4000 rad to primary. No difference at this level between aerobic and anaerobic irradiation.</td>
</tr>
<tr>
<td>1973</td>
<td>Sheldon and Fowler</td>
<td>118</td>
<td>Mouse</td>
<td>Lymphosarcoma</td>
<td>1000</td>
<td>Increase of metastatic lymph node size.</td>
</tr>
<tr>
<td>1974</td>
<td>Sheldon et al.</td>
<td>117</td>
<td>Mouse</td>
<td>Mammary carcinoma</td>
<td>Single and fractionated range</td>
<td>Increase of metastases in non-cured radiated mice. Authors state results inconclusive.</td>
</tr>
<tr>
<td>1975</td>
<td>Peters</td>
<td>99</td>
<td>Mouse</td>
<td>Squamous carcinoma</td>
<td>4500–6000</td>
<td>Improved survival with preoperative radiation. Diminished survival with sublethal dose presumed due to increased metastases.</td>
</tr>
<tr>
<td>1976</td>
<td>McCredie et al.</td>
<td>74</td>
<td>Mouse</td>
<td>Fibrosarcoma</td>
<td>4000</td>
<td>No difference in lung metastases between irradiated and amputated tumors. (Amputation 1 h after irradiation.)</td>
</tr>
<tr>
<td>1976</td>
<td>Sheldon and Fowler</td>
<td>119</td>
<td>Mouse</td>
<td>Mammary carcinoma</td>
<td>500 vs. 350 × 2</td>
<td>Slightly increased metastases in two-fraction group.</td>
</tr>
<tr>
<td>1977</td>
<td>Moore and Dixon</td>
<td>87</td>
<td>Rat</td>
<td>Mammary carcinoma</td>
<td>500–7000</td>
<td>Enhancement increasing with time from initial treatment.</td>
</tr>
<tr>
<td>Year</td>
<td>Authors</td>
<td>Species</td>
<td>Tumor Type</td>
<td>Preinoculation Dose</td>
<td>Effects Description</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>--------------------</td>
<td>---------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1977</td>
<td>van den Brenk et al.</td>
<td>Rat</td>
<td>Walker +</td>
<td>200 × 4</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Hahn et al.</td>
<td>Mouse</td>
<td>Osteosarcoma</td>
<td>3000 Preinoculation</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Rappaport and Brown</td>
<td>Mouse</td>
<td>Sarcoma</td>
<td>200 × 4, 600-3600</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>Rappaport and Brown</td>
<td>Mouse</td>
<td>Sarcoma</td>
<td>2400 Preinoculation</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Baker et al.</td>
<td>Mouse</td>
<td>Sarcoma</td>
<td>600 × 10</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Lord et al.</td>
<td>Dog</td>
<td>Osteosarcoma (spontaneous)</td>
<td>600 × 7 plus hyperthermia</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>DeRuiter et al.</td>
<td>Rat</td>
<td>Rhabdomyosarcoma</td>
<td>4500-8000</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>Dixon and Bagnall</td>
<td>Rat</td>
<td>Mammary carcinoma</td>
<td>500-4000</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>Todoroki and Suit</td>
<td>Mouse</td>
<td>Fibrosarcoma</td>
<td>2000-10,000 + Surgery</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>Todoroki and Suit</td>
<td>Mouse</td>
<td>Fibrosarcoma</td>
<td>3000-13,000 in five fractions + surgery</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Baumann et al.</td>
<td>Rat</td>
<td>Rhabdomyosarcoma</td>
<td>3000 Preinoculation</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Milas et al.</td>
<td>Mouse</td>
<td>Carcinoma</td>
<td>3000 Preinoculation</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Milas et al.</td>
<td>Mouse</td>
<td>Five carcinomas</td>
<td>2000 Preinoculation</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Ramsay et al.</td>
<td>Mouse</td>
<td>Fibrosarcoma and squamous cell carcinoma</td>
<td>5600-8500</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Hill and Denekamp</td>
<td>Mouse</td>
<td>SaF sarcoma</td>
<td>250–1000 + Miso and 4000</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Shen et al.</td>
<td>Mouse</td>
<td>Melanoma</td>
<td>6000/30 fr. vs. 3200/4 fr.</td>
<td>Decreased local tumor growth with increased metastases.</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>Baumann et al.</td>
<td>Mouse</td>
<td>Fibrosarcoma</td>
<td>One to 15 fractions: wide dose range</td>
<td>Increased mets with 15 fractions and/or low-dose/fraction in controlled tumor.</td>
<td></td>
</tr>
</tbody>
</table>

*Transplanted unless otherwise stated.  
*b Single doses unless otherwise stated.  
*c Control animals were sham-irradiated.
irradiated groups and, calculating for equal survival in each group, found a 'corrected' metastatic frequency of 17.7 per cent in the irradiated group compared to 4.5 per cent in the control group. A third experimental group was subjected to biopsy with a slight but non-significant increase of metastases.

Other investigators found a variety of responses to local tumor irradiation. Fisher and Fisher [39], for example, using identical experimental conditions when irradiating two different tumors, noted enhancement in one and no alteration of metastases in the other. Survival appeared similar between the groups while pulmonary metastases were significantly increased in the mammary carcinoma group. It was noted that the irradiated local tumor volumes were one-half of the control sham-irradiated tumors at the end of the observation period.

Suit et al. [129] studied the relationship of distant metastases to locally irradiated tumors given higher dosages with intent to produce a higher probability of local control. There was a significantly higher rate of pulmonary metastases in locally tumor-recurrent animals than in locally controlled animals.

Sheldon and co-workers [116,117] found inconclusive evidence for metastatic enhancement by local tumor irradiation. They considered that prolonged survival in irradiated groups, and large local tumor burdens in control groups, could both be factors in the observed metastasis enhancement rather than local tumor irradiation per se.

These possible influences on metastases were controlled in several investigations involving postirradiation surgical amputation of the tumor-bearing limb. McCredie et al. [74] amputated the tumor 1 h following irradiation and found no difference in metastasis between irradiated and non-irradiated limbs. Sheldon and Fowler performed surgical excision 24 h following single doses of 500 cGy or two fractions of 350 cGy. The latter group demonstrated a small but significant increase of pulmonary metastases compared to animals with unirradiated but surgically excised tumors [119]. Inch and McCredie [55], Van den Brenk and Sharpington [146], Crile and Deodhar [22] found decreased metastases in hosts receiving either postirradiation tumor amputation, or higher dosages, or treatment to smaller tumors.

The effects of fractionated irradiation were also considered in other investigations. Shen and co-workers irradiated a murine melanoma with daily fractions of 200 cGy to total 6000 cGy or weekly fractions of 800 cGy to total 3200 cGy, and observed for local tumor effect and metastases at 47 days after inoculation. There were significantly fewer metastases in the weekly fractions group as well as greater local tumor response [120]. Baumann, Suit and Sedlacek investigated the incidence of metastases after fractionated and single-dose irradiation of three early generation isotransplants of spontaneous tumors. Increased metastases were seen following curative fractionated (15 fractions) irradiation as compared to one or five fractions in one tumor, while low doses per fraction (200 Gy compared to 800 Gy) and longer interfraction times (48 h) were associated with a higher metastasis rate in another. As expected, non-curative irradiation was associated with higher metastasis rates. Neutron radiation yielded similar results [13].

Since the time factors appeared to be an important variable in metastasis rate a fixed observation period of 4 weeks following irradiation or amputation was established in experiments by Hunter et al. and Dubravsky et al. Single doses of 6000 cGy or isoeffective fractionated irradiations were used. The number of pulmonary metastases was significantly greater in the irradiated group although equally high rates of metastases (80–90 per cent) existed in both groups. The increase
Radiation enhancement of metastasis

of metastases was less marked following fractionated irradiation [54]. The injection of heat, irradiation, or sonically killed tumor cells into the opposite limb did not affect the number of metastases although steroids and Trasylol, an antifibrinolytic agent, did increase the number [33]. In two sets of experiments Todoroki and Suit used considerably larger doses of preoperative radiation either as single doses or with five daily fractions. In the single-dose experiments the rate of distant metastasis was significantly higher in animals receiving preoperative irradiation to 'small' tumors (44.8 per cent) compared to those receiving surgery only (21.1 per cent). These differences were found only in treatment failure mice presumably receiving lower radiation doses while the differences were less marked in 'large' tumors that were not locally cured [136]. Similar findings were stated for the five fraction experiments [137]. The authors believe these differences were due to longer survival times in the preoperative groups. However, tumor failure animals receiving radiation only had the highest rate of distant metastasis (57.1 and 55.6 per cent compared to 34.8 per cent in control animals) with survival times intermediate to the surgery only and the preoperative irradiation groups. Further experiments by the same group (Ramsay, Suit and Sedlacek) confirmed the high incidence of metastasis following failure of radiation therapy but also the significant reduction of distant metastasis by early salvage surgery [104].

Hill and Denekamp reported metastasis enhancement following local irradiation to subcurative doses with or without 'mild' hyperthermia in a mouse osteosarcoma [50]. Further data involving the study of mizonidazole and radiation indicated a light metastasis enhancement for low-dose radiation when given 2–3 days before curative doses of 4000 cGy compared to curative treatment alone (Sally Hill, personal communication, 14 April 1989). Enhanced metastatic rates in both irradiated and sham-irradiated animals were noted by Baker et al. [7]. Enhanced metastases following local irradiation with hyperthermia to a spontaneous canine osteosarcoma when compared to historical control were found by Lord et al. [71]. DeRuiter et al. noted varying effects on a variety of rodent tumors. This investigation involved a study of the influence of heavily irradiated normal tissues in a non-tumor-bearing site with transplantation of irradiated tumor to an amputation site. They concluded that both factors (irradiated normal tissue and irradiated tumor) were essential to the enhancement phenomenon [28].

A number of other investigators, including van den Brenk, Rappaport, Milas and co-workers, have focused on the so-called tumor bed effect with the following findings: preirradiation of the tumor transplant site leads generally to a reduced growth rate of the tumor implant. In those cases exhibiting delayed outgrowth (tumor bed effect) an enhancement of both incidence and growth rate of regional or distant metastases could be demonstrated [80, 84, 105, 106, 142].

Possible mechanisms

From the experimental data it can be seen that the incidence of metastasis following local tumor irradiation can be increased following local tumor irradiation nearly only with doses insufficient to cure the primary tumor. A number of additional experimental conditions need to be considered when proposing mechanisms. These include the spontaneous metastasis rates, clonogenic tumor burden, effect of sham-irradiation, growth delay by irradiation and survival time.
Four possible mechanisms which might influence the rate of metastasis following local tumor irradiation can be considered:

1. Direct alteration of clonogenic tumor cells by irradiation leading to an enhanced ability to metastasize.
2. Abscopal effect of local irradiation leading to enhanced capability of distant sites to support metastasis.
3. Local effect of irradiation facilitating entry of tumor cells into the circulation.
4. Local effect of irradiation delaying tumor progression thus allowing increased time for escape of tumor cells into the circulation.

**Direct alteration of tumor cells by irradiation.** Could a process of mutagenesis or other cellular change play a role in altered metastatic behavior following irradiation? One experiment directly addressed this question by transplanting metastatic lung nodules developing in animals receiving local tumor radiation to non-irradiated recipients. No enhancement of metastatic capacity was detected in the first-generation transplant [151]. The number of transplanted recipients, however, was small. Evidence that radiation can enhance progression of malignant behavior of tumor cells has been found following radiation of mouse skin tumors [58]. Fibrosarcoma cells exposed to UV radiation in vitro demonstrated enhanced metastases following implantation [40]. *In vitro* experiments by Young and co-workers employing hypoxic exposure to murine tumor cells showed a transient enhancement of metastatic potential of over 10-fold by 18 h following reoxygenation in an artificial metastasis (i.v. injection) system [163]. This effect appears unrelated to cell cycle perturbation. Reoxygenation of previously hypoxic tumor cells is known to occur following fractionated radiation. Beck-Bornholdt with Baumann and co-workers carried out flow cytometric measurements over time during fractionated radiotherapy and were able to correlate changes in the DNA of cells in metastases with those in the primary irradiated tumors. They believed that this technique was useful in timing the onset of metastatic spread [12, 14]. The findings do not, however, implicate any altered metastatic behavior in the cells removed from the pulmonary metastases. Talmadge and Fidler did find an enhanced metastatic capacity in cells harvested from spontaneous metastases [131]. Radiation may alter the internal inhomogeneous cell environment of a tumor thus allowing selection for the more invasive, potentially metastasizing cell to proliferate. Such a selection process could be determined by cytometry and retransplantation assay methods noted above [131, 151].

**Abscopal effect of local irradiation.** Does local radiation alter the ability of distant sites to support metastatic localization? This has been studied by radiation of non-tumor-bearing areas and comparison of metastatic incidence with recipients receiving local tumor irradiation. The results of one experiment indicate no such effect [151]. Experiments by de Ruiter et al., however, noted a small but significant enhancement of metastases when a non-tumor-bearing leg was irradiated simultaneously with inoculation of irradiated tumor cells into the opposite amputation site [28]. No sham irradiation control experiment, however, was performed, a possible significant factor in metastasis enhancement which will be further discussed. Dubravsky et al. injected heavily irradiated or sonicated tumor cells into tumor-bearing animals but found no metastasis enhancement [33].
Local effect of irradiation facilitating entry of tumor cells into the circulation. Does irradiation of the tumor bed (or stroma) enhance the escape of cells into the circulation? Van den Brenk and co-workers transplanted tumor cells into a site that had previously received 3000 cGy. There was an enhancement of regional lymphatic metastases compared to transplants into unirradiated tissues [142]. They postulated that irradiation of the tumor bed led to an accelerated loss of viable tumor cells from the site of inoculation and thus enhanced lymphatic dissemination. The intravasation of cancer cells has been extensively studied, and appears to involve degradation of the extracellular matrix of blood vessels, the basement membrane (see reviews by Roos and Dingemans [111], and by Weiss et al. [156]). Heisel and co-workers developed an in vitro blood vessel wall system. They demonstrated that preirradiation enhanced the ability of tumor cells to degrade the blood vessel wall system [46].

Another possible factor was studied by Bonfil and co-workers, who injected extracts of necrotic tumors into non-metastasizing but related tumors with resultant metastases [15]. Cytotoxic therapy, such as irradiation, produces cell death leading to necrosis, a possible prometastatic factor.

Inhibition of the host desmoplastic response to tumor growth by a collagen synthesis inhibitor was shown to enhance metastases in a study by Barsky and Gopalakrishna [10]. The role of irradiation in desmoplastic reactions is poorly understood.

The possible effect of radiation directly on the stroma and microvasculature to facilitate intravasation of tumor cells is presently conjectural and requires further study.

Local effect of irradiation delaying tumor progression, thus allowing increased time for escape of tumor cells into the circulation. Does irradiation of the tumor produce growth inhibition, thus prolonging host survival and therefore the time period during which metastasis can develop?

In a series of studies involving a variety of tumors, Milas and co-workers challenged the concept by van den Brenk et al. [142] of increased escape of cells, on the grounds that not all tumors demonstrated metastasis enhancement. Those tumors exhibiting metastasis enhancement also demonstrated the tumor bed effect, i.e. reduced growth rate. Metastases developed only after tumors reached approximately 7 mm in diameter. It was calculated that there was a constant release of metastatic cells per unit time for both irradiated and unirradiated transplantation sites, thus indicating that growth delay of tumors in the irradiated site was responsible for the increased number of metastases [80].

These conclusions were supported by the observations of Ramsay and co-workers in experiments on two transplanted tumors comparing metastasis rates of irradiated or resected tumors with those of recurrent tumors following radiation failure. The metastasis incidence was enhanced following local failure while curative radiation and curative surgery yielded similar lower rates. The metastasis incidence was definitely higher with tumor size. Early 'salvage' surgery yielded much lower rates of metastasis than 'late' surgery. The growth rate of recurrent tumors was much less than that of primary tumors and the authors believe that the metastasis rates could be explained by the longer time interval taken by recurrent tumors to reach a given size [104].

Thus observations in both a tumor-bed-effect system and a tumor system indicated that enhanced metastasis following local irradiation could be explained by
the longer time interval available to regrowing tumors following radiation. Certain other experiments, however, were designed to control this time difference, and yet showed increased metastasis rates in the irradiated groups. von Essen and Kaplan equalized the survival among animals in these experimental groups by matched sacrifice of experimental animals [151] and found a four-fold increase in the irradiated groups.

Kaae analyzed and compared the rate of metastasis according to survival between the groups receiving local tumor irradiation and the controls. He concluded that there was a real increase in the metastatic frequency following local irradiation of the tumor at a single dose of 1000 to 2000 cGy [59].

Hunter et al. randomized animals to receive local tumor irradiation or surgery at 16–20 days following transplantation, then sacrificed all animals at 28 days following treatment. The incidence of occurrence of pulmonary metastasis was similar in both groups (80–90 per cent) but the number of metastases in the lungs was significantly higher in the irradiated group. There was, however, no untreated control group [54].

The clonogenic tumor cell burden is largely unknown in the experiments quoted. Since metastasis appears related directly to the number of clonogenic cells, experiments employing clonogenic assay appear necessary in order to determine the relative roles of vascular–stromal damage and tumor shedding of viable cells.

Clinical relevance

There are no clinical data clearly indicating that the successful radiation therapy of tumors can be prometastatic. Such an effect, if it exists, must be small and would be exceedingly difficult to prove, given the marked diversity of human tumor response and behavior. There have been clinical observations, however, suggesting unusual metastatic behavior following inadequate radiation therapy or following relapse.

Kaplan and Murphy developed their laboratory experiments upon clinical observations of unusually early and widespread metastases following inadequate radiation therapy of carcinoma of the lip and buccal mucosa [62]. Fisher and Fisher reviewed some prior clinical impressions regarding enhanced metastases following radiation therapy for breast cancer [39]. Stjernswärd implicated routine postoperative radiation therapy as leading to increased mortality in early-stage cancers, presumably because of increased distant metastases [126]. The underlying mechanism inferred was radiation-induced immunosuppression. This effect was supported in a hypothesis by Papaioannou [97]. There was no experimental evidence, however, to confirm immunosuppression by local tumor radiation therapy as a factor in enhanced metastases. A controversy developed over this topic, with numerous arguments for and against radiotherapy as a prometastatic agent. Finally Zubiana, in a comprehensive review of clinical data, demonstrated that there was no evidence for enhancement of metastasis by irradiation. The initial contention by Stjernswärd, nevertheless, was subsequently confirmed, in part, by Cuzick et al. with respect to increased mortality in one irradiated group after 10 years [23]. The causes of this increased mortality, however, are not yet available although early data (Cuzick, J., personal communication, 20 August 1988) suggests cardiac disease.

De la Monte and co-workers studied the results of post-mortem examinations of 85 patients dying with small cell carcinoma of the lung [27]. They correlated patterns of metastatic involvement with the form of treatment. These patterns differed significantly with treatment modality including radiation alone, chemotherapy alone
Radiation enhancement of metastasis

or combination therapy. Twenty-eight patients received no therapy. Although survival was prolonged with therapy, there was no difference in the number of metastases. The metastatic pattern, however, was different for each therapeutic modality. Patients receiving radiation therapy only had more extensive or more frequent metastases to the adrenal glands, pancreas, colon, and cerebral white matter than those treated by other modalities or who received no treatment. The authors proposed that specific treatments may modify the behavior of the primary tumor through mutation or selective growth advantage of certain subpopulations. Similarly, altered patterns of metastases have been seen following various regimens of therapy for breast cancer [60].

In the area of head and neck cancer, speculation has been raised regarding the prometastatic effects of adjuvant radiotherapy and/or chemotherapy. These data are summarized in table 3. Merino et al. reviewed over 5000 cases of head and neck cancer, noting that autopsy data in 1923 showed a 1 per cent incidence of distant metastases in patients dying of head and neck cancer. In their present study there was about a 10 per cent overall incidence at autopsy with 16.7 per cent distant metastases with uncontrolled disease above the clavicle and 7.9 per cent when there was no locoregional recurrence or persistence. The rates appeared independent of treatment modality. However, an unexpected finding was a doubling of incidence (to 20 per cent) when postoperative radiotherapy was given to T3-4, N2-3 cases. The local control rate, however, was higher with postoperative radiotherapy than with surgery alone, or with preoperative radiotherapy [78]. A randomized trial comparing preoperative radiotherapy with surgery alone in 97 oro- and hypopharyngeal cancer [128] demonstrated no difference in local disease control with a small but significant difference in cases demonstrating distant metastases (one of 44 for surgery alone, six of 42 for preoperative radiotherapy, \( P = 0.003 \)). A second randomized trial with similar sites and strategy involving 248 patients showed no significant differences in local control or distant metastases between the two groups [134]. Analysis of the results of non-randomized adjuvant therapy programs generally indicated a higher distant metastasis rate in the groups receiving one or more adjuvant therapies than those receiving surgery alone [52, 89, 149] or radiation alone or with salvage surgery [124].

These findings were reviewed by Schantz and Goepfert [112] and interpreted with respect to their own series of 196 patients. Stratification by natural killer cell activity demonstrated, according to the authors, a tendency to develop distant metastases with lower natural killer cell activity following adjuvant therapy. They concluded that three factors were necessary to demonstrate a high risk of distant metastases: nodal metastases, low natural killer cell activity, and adjuvant radiation therapy.

The failure of randomized trials of adjuvant therapy for head and neck cancer to achieve a survival advantage over conventional surgery alone was discussed by Tannock and Browman, with the suggestion that chemotherapy may lead to increased distant metastases [133].

Analysis by McMillan and Hart [76], and a hypothesis by Kerbel and Davies [64] that cancer therapy may facilitate tumor progression, have focused on data involving chemotherapy. Despite a diligent search there has been no other clinical evidence found for a possible prometastatic effect by radiation therapy of tumors. Definitive radiation therapy produces a far greater tumor lethal effect than can generally be achieved by chemotherapeutic regimes. Thus the clonogenic fraction of tumor cells...
Table 3. Local tumor irradiation and metastatic behavior in head and neck cancers.

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Ref.</th>
<th>Form of study</th>
<th>Treatment (doses in cGy)</th>
<th>Rate of distant metastasis (DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>Merino et al.</td>
<td>78</td>
<td>Retrospective</td>
<td>Radiation or surgery or surgery + radiation</td>
<td>No differences between radiation and surgery. Two-fold increase in postoperative group.</td>
</tr>
<tr>
<td>1978</td>
<td>Strong et al.</td>
<td>128</td>
<td>Prospective, Randomized</td>
<td>Surgery vs. preoperative radiation (2000/5 fractions)</td>
<td>86 evaluable cases. 1 DM in surgery group and 6 DM in preoperative group at 3 years.</td>
</tr>
<tr>
<td>1978</td>
<td>Terz et al.</td>
<td>134</td>
<td>Prospective, Randomized</td>
<td>Surgery vs. preoperative radiation (1400/2 fractions)</td>
<td>248 cases. No difference in DM.</td>
</tr>
<tr>
<td>1984</td>
<td>Slotman et al.</td>
<td>124</td>
<td>Prospective, not randomized</td>
<td>4500–7000 in combined chemotherapy–radiation–surgery protocol</td>
<td>40% DM patients receiving chemotherapy–radiation surgery vs. 12.5% receiving radiation + surgery. No disease-free survival difference at 1 year.</td>
</tr>
<tr>
<td>1984</td>
<td>Vikram et al.</td>
<td>149</td>
<td>Retrospective</td>
<td>Surgery vs. surgery + radiation</td>
<td>18% DM on combined group compared to 4% in historical surgery-only group.</td>
</tr>
<tr>
<td>1985</td>
<td>Hong et al.</td>
<td>52</td>
<td>Prospective, non-randomized</td>
<td>Chemotherapy–radiation-surgery or chemotherapy–radiation/6000</td>
<td>26% DM overall. No reduction by chemotherapy of DM.</td>
</tr>
<tr>
<td>1986</td>
<td>O'Brien et al.</td>
<td>89</td>
<td>Retrospective</td>
<td>5000–6500 pre- or postoperatively</td>
<td>18% DM in radiation group compared to 4% in surgery-only group. Overall recurrence and survival rates in both groups similar.</td>
</tr>
<tr>
<td>1987</td>
<td>Schantz and Goepfert</td>
<td>112</td>
<td>Retrospective</td>
<td>Surgery vs. surgery + radiation</td>
<td>16% DM for surgery alone vs. 60% for surgery + radiation.</td>
</tr>
</tbody>
</table>
remaining in a tumor may be the single most important factor in the metastasis process following any form of treatment, regardless of the various mechanisms discussed.

The clinical experience that failure to control local disease is associated with increased distant metastases has been a recognized maxim in clinical oncology. Anderson and Dische demonstrated this in their study of local control failures following radiation therapy of cervix cancer [3].

Discussion

There is little or no evidence to indicate that local tumor irradiation in experimental tumor systems involves a genetic change of tumor cell behavior, a process of clonogenic selection, or immunodeficiency permitting increased metastasis. The principal question remaining concerns whether tumor cells are actually accelerated into the circulation by irradiation or if the radiation-induced growth delay permits a longer time for cells to metastasize. There is conflicting evidence concerning these two possible effects.

The tumor-bed-effect (TBE) system permits observations to be made of host response to irradiation and the subsequent effect of a growing tumor implant in this environment. The work by Milas and co-workers indicates that where growth delay of a tumor graft implanted into irradiated tissue occurs, the number of metastases is enhanced. The results found in this particular experimental system may not necessarily apply, however, to a tumor irradiated in situ. In the latter system several investigators found an enhancement of metastasis at fixed time-points or under conditions of equal survival [54, 59, 151]. It has been found that tumor size per se is correlated with metastasis [159]. Paradoxically a local tumor mass may inhibit growth of metastases [42] and its removal may enhance growth kinetics of residual, e.g. metastatic tumor [43, 157]. Voutilainen, however, demonstrated reduced growth kinetics of peripheral tumor sites following local tumor irradiation [153]. Fisher et al. noted the opposite effect, i.e. increase of labelling index in metastatic tumors following 5000 cGy local irradiation to the primary tumor [38]. Many of the experiments included measurements of the irradiated and unirradiated tumors. The size of the irradiated tumor was always smaller, yet the number of metastases was greater in the irradiated group. Thus, the two factors known to influence metastasis, tumor size and tumor age, may have varying effects upon metastasis in addition to the possible direct action of irradiation upon the tumor vasculature permitting an increased escape of cells into the circulation or even other mechanisms previously discussed involving hypoxia and reoxygenation or tumor necrosis.

In most of the experiments, however, there was stress due to trauma of immobilization, manipulation of the tumor, or of anesthesia, all factors that have been implicated in enhancement of metastasis [4, 7, 63]. The control groups were seldom subjected to sham procedures, and thus this important influence cannot be ruled out completely, although several experiments involved sham-irradiation. One of these, but not the others, noted equal metastasis enhancement by sham procedures.

Effects of normal tissue irradiation on localization of metastases

In contrast to the data on local tumor irradiation, there are numerous clinical as well as experimental observations on the localization of metastases in irradiated normal tissues. Table 4 summarizes the available information on this latter effect.
Table 4. Effects of normal tissue irradiation upon metastatic behavior.

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Ref.</th>
<th>Host</th>
<th>Tumor*</th>
<th>Irradiated tissue</th>
<th>Dose (cGy)*</th>
<th>Effects of radiation compared to non-irradiation control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1935</td>
<td>Schurch</td>
<td>113</td>
<td>Human</td>
<td>Gastric carcinoma</td>
<td>Skin</td>
<td>2400/4 weeks</td>
<td>Metastasis confined to target tissue.</td>
</tr>
<tr>
<td>1935</td>
<td>Schwarz</td>
<td>114</td>
<td>Human</td>
<td>Breast carcinoma</td>
<td>Skin</td>
<td>1500/10 fractions</td>
<td>Metastasis confined to target tissue.</td>
</tr>
<tr>
<td>1961</td>
<td>Woodruff</td>
<td>160</td>
<td>Human</td>
<td>Melanoma</td>
<td>Skin</td>
<td>?</td>
<td>Metastasis confined to target tissue.</td>
</tr>
<tr>
<td>1961</td>
<td>Dao and Moore</td>
<td>25</td>
<td>Human</td>
<td>Breast carcinoma</td>
<td>Skin</td>
<td>4500/3 weeks</td>
<td>Massive dermal metastases confined to irradiated skin</td>
</tr>
<tr>
<td>1962</td>
<td>Dao and Kvaric</td>
<td>24</td>
<td>Human</td>
<td>Breast carcinoma</td>
<td>Skin and lung</td>
<td>4500/3 weeks</td>
<td>Increased metastases in target tissue.</td>
</tr>
<tr>
<td>1963</td>
<td>Koike et al.</td>
<td>66</td>
<td>Mouse</td>
<td>Ehrlich ascites*</td>
<td>Liver</td>
<td>1500</td>
<td>Increased metastases with prior irradiation.</td>
</tr>
<tr>
<td>1967</td>
<td>Dao and Yogo</td>
<td>26</td>
<td>Rat</td>
<td>Mammary carcinoma</td>
<td>Lung</td>
<td>500-2000</td>
<td>Five-fold increase with prior irradiation.</td>
</tr>
<tr>
<td>1969</td>
<td>Fisher and Fisher</td>
<td>39</td>
<td>Mouse</td>
<td>Walker tumor*</td>
<td>Lung and liver</td>
<td>1000-2000</td>
<td>Increase size and number with irradiation 1-7 days prior to i.v. and intraportal injections.</td>
</tr>
<tr>
<td>1970</td>
<td>Zeidman and Fidler</td>
<td>164</td>
<td>Rabbit</td>
<td>V2 carcinoma*</td>
<td>Whole body</td>
<td>400</td>
<td>Increased lung metastases with prior irradiation.</td>
</tr>
<tr>
<td>1971</td>
<td>Cole and Halnan</td>
<td>20</td>
<td>Human</td>
<td>Breast carcinoma</td>
<td>Skin</td>
<td>3500-4000/3-4 weeks</td>
<td>Four cases of metastases confined to target tissue.</td>
</tr>
<tr>
<td>1972</td>
<td>Fidler and Zeidman</td>
<td>36</td>
<td>Rabbit</td>
<td>V2 carcinoma*</td>
<td>Whole body</td>
<td>450</td>
<td>Increased radioisotope labelled tumor cells in irradiated tissue.</td>
</tr>
<tr>
<td>1973</td>
<td>Owen and Bostock</td>
<td>96</td>
<td>Dog</td>
<td>Melanoma* + osteosarcoma</td>
<td>Lung</td>
<td>1200</td>
<td>Reduction if radiation followed i.v. injection or ablation. Enhancement in four cases where primary was not controlled.</td>
</tr>
<tr>
<td>1973</td>
<td>van den Brenk et al.</td>
<td>141</td>
<td>Mouse</td>
<td>Sarcoma*</td>
<td>Lung, liver</td>
<td>1000-1500</td>
<td>Increased metastases with prior irradiation.</td>
</tr>
<tr>
<td></td>
<td>van den Brenk and Kelly</td>
<td>143</td>
<td>Rat</td>
<td>Walker tumor*</td>
<td>Kidney</td>
<td>1000-3000</td>
<td>Ten-fold increase with prior irradiation.</td>
</tr>
<tr>
<td>1973</td>
<td>Withers and Milas</td>
<td>158</td>
<td>Mouse</td>
<td>Fibrosarcoma*</td>
<td>Lung</td>
<td>200-300 (whole-body)</td>
<td>Killed C. granulosum protected from enhanced metastases.</td>
</tr>
<tr>
<td>1974</td>
<td>Milas et al.</td>
<td>83</td>
<td>Mouse</td>
<td>Fibrosarcoma*</td>
<td>Lung</td>
<td>1250 or 5 × 350</td>
<td>Increased metastases; fractionated dose more effective than single dose.</td>
</tr>
<tr>
<td>1974</td>
<td>van den Brenk and Kelly</td>
<td>144</td>
<td>Rats</td>
<td>Walker tumor*</td>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Species</td>
<td>Tumor Type</td>
<td>Site</td>
<td>Dose (Range)</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>------------------</td>
<td>----------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>Mouse</td>
<td>Fibrosarcoma*</td>
<td>Large</td>
<td>300-1500</td>
<td>Radiation volume-dependent increased tumor growth outside target volume.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>Thompson</td>
<td>Mammary carcinoma*</td>
<td>Lung</td>
<td>250-2000</td>
<td>Increased metastases; effect seen with doses up to 9½ month gap.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>Peters</td>
<td>Chondrosarcoma</td>
<td>Lung</td>
<td>1600-2000</td>
<td>Increased metastases with 5-week gap.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td>Owen</td>
<td>Various</td>
<td>Lung</td>
<td>600-1200</td>
<td>Increased metastases in two of three spontaneous tumors.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>Stjernswärd and Douglas</td>
<td>Human Breast carcinoma</td>
<td>Various sites</td>
<td>4000-5000</td>
<td>Eight cases of metastases confined to target tissue.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1976</td>
<td>Tanaka</td>
<td>Ehrlich carcinoma*</td>
<td>Lung</td>
<td>1000-3000</td>
<td>Linear relationship of dose to metastases enhancement.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>Shewell</td>
<td>Spontaneous mammary carcinoma</td>
<td>Lung</td>
<td>500</td>
<td>Two-fold or greater enhancement in irradiated lung.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Dubravsky et al.</td>
<td>Mouse Fibrosarcoma*</td>
<td>Lung</td>
<td>1000-3000</td>
<td>Artificial metastasis enhanced by prior irradiation. ‘Spontaneous’ metastasis not enhanced.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>Marley and Marley</td>
<td>Human Uterine carcinoma</td>
<td>Skin</td>
<td>4000 + 2000</td>
<td>Metastases appeared first in irradiated skin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Suzuki</td>
<td>Mouse Fibrosarcoma</td>
<td>Lung</td>
<td>500/whole body</td>
<td>Artifical metastases enhanced, spontaneous metastases reduced.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>Hirata and Tanaka</td>
<td>Human tumor* cell lines</td>
<td>Lung</td>
<td>2000</td>
<td>Increased metastases with prior irradiation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>Ito et al.</td>
<td>Human Breast carcinoma</td>
<td>Skin</td>
<td>6000/6 weeks</td>
<td>Metastases appeared first in irradiated site.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>Diehl et al.</td>
<td>Human Breast carcinoma</td>
<td>Skin</td>
<td>5000/5 weeks</td>
<td>Two cases of selective localization.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 'Artificial' metastases system (i.v. injection of tumor cells). b Single doses unless otherwise stated.
The first report, by Schurch in 1935, described the appearance of metastases from a carcinoma of the stomach to the skin of the back in an area geographically conforming to a previous field of postoperative radiotherapy given 19 months previously to an exposure of 2400 rads to the skin in 11 fractions over 26 days \[113\]. The author speculated that metastatic cells localized to an area of reduced resistance due to radiation damage in a way similar to previously known occurrences of metastases to traumatically damaged tissues.

Dao and his colleagues 25 years later focused attention on this effect in a series of clinical reports documenting the apparent localization of metastases from primary breast cancer in irradiated skin and lung \[24, 25\]. These reports were followed by further clinical observations and by experimental studies. These have been reviewed in 1978 \[152\] and in 1984 \[86\]. Since the latter review by Milas and Peters, there have been few additional investigations and clinical case reports to alter their conclusions substantially. However, a diligent literature search has been made in order to complete the picture and these additional citations are included \[25, 30, 51, 56, 73, 77, 90, 120, 130, 132, 138, 141, 160\] that were not listed in the two indicated reviews.

The conclusions of the two reviews remain largely valid and will be summarized with comments based upon the additional citations listed above.

**Experimental studies**

The experimental studies can be divided into two groups: one employing a system of intravenous injection of tumor cells to produce distant metastases—the artificial metastasis method; the other the spontaneous metastasis method. These are identified in table 4 by asterisks (the artificial system) following the description of the tumor. It can be seen that the vast majority of studies were performed with the artificial metastasis method which had the advantage of better experimental control and a higher yield of metastasis limited to the lungs, which were the principal target organs studied. The conclusions based principally upon the artificial metastasis system are as follows.

The radiation enhancement of subsequent metastases predominantly to the lungs appears related to local rather than systemic effects. The effect is dose-related and has a complex time relationship with a maximum at 1 day after radiation but with a second peak possible after several months. Longer entrapment of cells in radiated tissue appears to be the principal initiating event leading to enhanced metastasis formation. The effect was found to occur only if there was a source of cancer that was shedding cells into the circulation, or if cancer cells were artificially introduced into the circulation following irradiation of the target tissues. It was much less pronounced under conditions of spontaneous metastases \[120\], or even reversed with whole-body irradiation of animals bearing transplanted fibrosarcomas \[130\] or when the primary tumor was excised *prior* to the radiation exposure to the target organ \[115, 138\]. However, several studies confirmed enhanced pulmonary metastases in irradiated lung under conditions of spontaneously metastasizing cells \[96, 98, 121\].

The necessary conditions of viable cells circulating at or following the time of irradiation with a peak effect 1 day after radiation, along with a direct dependence on dosage, suggested to many investigators that an inflammatory reaction in the vasculature acted as a support for tumor cell lodgement and subsequent growth.
Possible mechanisms

1. **Immunosuppression.** A systemic immunosuppression effect by irradiation can be considered possible as a mechanism of metastasis enhancement. Eccles and Alexander found such an effect following whole-body irradiation in rats with recently surgically removed syngeneic sarcomas [34]. Metastases were increased in both lymph nodes and lungs. Hewitt and Blake reversed the experimental design by transplanting a murine carcinoma between 1 and 90 days following whole-body irradiation [47]. Because they found a metastasis enhancement effect over this long time interval, a mechanism other than immunosuppression was considered likely. Most experiments, however, have involved localized radiation, typically hemithoracic radiation and metastasis enhancement has been noted only within the irradiated tissue, an effect tending to argue against systemic immunosuppression, at least for localized radiation.

   Natural killer (NK) cells have been considered as antagonists to metastatic spread [45]. Nlibe and Poupon demonstrated enhancement of pulmonary metastasis following cytotoxic reduction of NK cell activity [88]. Milas and Peters demonstrated a reduction of NK cell activity by whole-body, but not by thoracic radiation [86]. Hirato and Tonaka, however, measured a lower NK activity in lungs receiving hemithoracic radiation [51].

   The roles of NK and other host defense components in metastasis formation are not yet fully understood. They should be included in future radiation studies.

2. **Local tissue damage.** The possibility that the metastasis-enhancing effect is limited to the radiated tissue is a compelling argument. von Essen and Stjernsward [152] and Milas and Peters [86] presented the evidence in considerable detail.

   The extracellular matrix of the capillary wall appears to be a site of preferential localization of tumor cells [65, 67, 69, 150]. Agents that damage the overlying endothelium have been associated with increased attachment of tumor cells [94, 130]. An artificial blood vessel system in vitro had increased degradation by tumor cells following irradiation [46]. A transient increase of vascular permeability allowing migration of trapped tumor cells into the perivascular connective tissue was postulated [132] but this does not explain the biphasic effect with a second peak many months later [158]. Clearance of tumor cells from lungs was shown to be delayed by prior irradiation [79, 100].

   Another possible mechanism is the ‘feeder’ effect originally described by Revesz [107]. Heavily irradiated cells admixed with tumor cells result in increased metastases in some [48, 85], but not in other [122] tumor systems. Other effects noted in irradiated normal tissue, such as dermatophytosis [72] or graft v. host disease [165], suggest factors that may encourage the localization and growth of circulating tumor cells as are seen sometimes in sites of traumatic injury (locus minoris resistentiae).

**Clinical relevance.** The clinical findings that metastases occasionally appear initially or preferentially in previously irradiated tissues have been documented, as shown in table 4, in 12 reports. In seven of these the primary tumor was carcinoma of the breast, and radiation therapy was delivered locally following mastectomy. The interpretation that radiation enhanced the metastases to irradiated chest wall skin.
must be made with caution, since permeation of dermal lymphatics prior to surgery and radiation probably existed in most cases. Several individual illustrations of apparent confinement of dermal metastases within the rectilinear geographic outlines of the fields of irradiation suggest, however, that some process favoring tumor growth or localization in irradiated normal tissue was involved.

More compelling evidence, however, is seen in cases where the radiated tissues were very probably not already infiltrated with tumor cells, and where the primary tumor was relatively remote from the irradiated target tissues that subsequently demonstrated metastases. These case reports include a variety of primary tumors [73, 77, 90, 113, 159]. It can be seen that this phenomenon is rare in clinical medicine. Many papers quoted in the two reviews refuted or failed to confirm these findings. The treatment factors were varied and no single factor can be isolated, although in some reports there was a high proportion of patients with severe radiation injuries, indicating radiation overdosage [24, 25].

The clinical consequences of lung irradiation were critically addressed by Peters and co-workers [101], who did not find convincing evidence for an enhancement of pulmonary metastases by irradiation. They postulated that irradiation or surgical removal of the primary disease effectively reduced clonogenic circulating tumor cells before significant conditioning of the normal tissue can take place.

A tenuous strand of data from recent clinical trials was provided by the Gastrointestinal Tumor Study Group (GITSG), protocol 6179, comparing prophylactic hepatic irradiation (2100 cGy) plus 5-fluorouracil versus no adjuvant therapy in patients with resected Stage B2 or C colon cancer (table 5). There were slightly more recurrences in the control group (55/132, 36 per cent) compared to the experimental group (47/152, 31 per cent), but fewer hepatic metastases (16/153, 29 per cent) compared to the experimental group (22/152, 47 per cent). There were, however, two therapeutic agents applied in the experimental group, thus rendering any determinations of causal effect, even despite the marginal differences, inconclusive. This trial has been discontinued (Robert J. Mayer, personal communication, 16 November 1987).

It is therefore only possible to speculate that, on the basis of the experimental data, there may be a potential risk in prophylactic irradiation of normal structures under conditions of a high risk of persistence or recurrence of a potentially highly

Table 5. GITSG adjuvant colon cancer protocol comparing hepatic irradiation + 5-FU to control.

<table>
<thead>
<tr>
<th>Pattern of failure</th>
<th>Control</th>
<th>Radiation therapy (2100 rad) + 5-fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. evaluable</td>
<td>153</td>
<td>152</td>
</tr>
<tr>
<td>No. recurrences</td>
<td>55 (36%)</td>
<td>47 (31%)</td>
</tr>
<tr>
<td>No. local</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>No. distant</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>No. local and distant</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No. any liver</td>
<td>16 (29%)</td>
<td>22 (47%)</td>
</tr>
</tbody>
</table>

Median follow-up time = 32 months.
Radiation enhancement of metastasis

metastatic primary tumor. Even this speculative caution has not been supported by any data so far, for example, in the prophylactic irradiation of the brain in cases of small-cell carcinomas of the lung.

Discussion. The extensive experimental data support the phenomenon of enhancement of pulmonary metastases by prior irradiation of the lungs. This is more frequently observed following intravenous injection of tumor cells (artificial metastasis method) than by spontaneous metastases from transplanted or spontaneous tumors. The mechanisms appear related to a local vascular damage, possibly of endothelial cells, permitting tumor thrombi to invade the extracellular matrix of the vessel walls. Other possible mechanisms—such as fibrinolysis, clot formation, growth in damaged tissues, growth stimulation of tumor cells and immunosuppression—have been considered in this paper, by Milas and Peters [86], and in a review by Roos and Dingemans [111], and all have been considered less likely. There is nothing to contest the possibility that several mechanisms may be operative under differing conditions.

The clinical evidence is scanty and chiefly documented for the skin in case reports. The experimental evidence is compelling to lead several authors (Piro and Hellman [102], Peters et al. [101], Milas and Peters [80], von Essen and Stjernswärd [152]) to recommend caution in new ventures in radiation therapy methodology.

Conclusions

Like all therapeutic modalities, radiation therapy is a two-edged sword. Toxicity to normal tissues has been usually considered the shadow of therapeutic benefit. A further rare untoward effect may be the enhancement of metastases by irradiation.

The experimental evidence for metastasis enhancement by local tumor irradiation suggests two mechanisms: (1) a radiation-induced growth delay mediated by stromal and/or tumor cell damage permitting a constant rate of escape of tumor cells into the circulation over prolonged time periods; (2) vascular damage permitting an increased rate of escape of tumor cells. The effect occurs principally, but not exclusively, with subcurative radiation doses.

It would seem timely to perform specifically designed experiments to control the possible influences of stress, tumor type, size, and age, and the possible selective or mutational influences of irradiation on the unstable, heterogeneous tumor cell population. A radiation dose–response experiment with controlled survival, sham-irradiated controls, and subsequent transplantation of metastases would help to resolve the issue of whether radiation may actually increase the escape of metastatic cells or, by growth inhibition, allow a longer time for tumor cells to escape to metastatic sites, or somehow alter the metastasis potential of irradiated cells.

The experimental evidence for enhanced localization of metastases in irradiated normal tissues suggests one likely mechanism: local vascular damage permitting tumor cells to attack and invade the extracellular matrix of the vessel wall.

The phenomenon requires radiation to the normal tissue, principally lungs, prior to circulation of tumor cells in the bloodstream. This occurs less often with spontaneous metastasis than with artificially injected tumor cells into the circulation. Damage to other defenses, such as natural killer (NK) cells, should be considered.

The clinical occurrence of the first phenomenon has yet to be proved. Some suggestive evidence, however, leads to concern that subcurative irradiation may enhance metastases. The second phenomenon has been documented in the case of
skin metastases but for no other site. Again concern exists that prophylactic (elective) irradiation of normal tissue in the presence of potentially persisting or recurring metastasizing tumor may be deleterious. A large difference between experimental animal tumor systems and human cancer with respect, at least, to the phenomena discussed here, probably exists.

As therapeutic methods achieve better rates of local tumor cure, the problem of metastases becomes more prominent. Efforts to prevent or eliminate distant metastases therefore must be increased. A more effective systemic therapy is desirable, but of comparable importance is the prevention of metastases. Increasing knowledge of the unstable and heterogeneous nature of cell population in tumors suggests that prometastatic influences may come from a variety of sources, even including therapeutic modalities themselves.

A review of the published results of clinical trials indicates a sparsity of documentation of metastases in time and by site following therapy. Since chemotherapy and other modalities have also been shown experimentally to enhance metastasis under certain conditions, an increased effort appears indicated to study patterns of failure, particularly the time and site of appearance of distant metastases, in order to determine the existence and significance of untoward patterns of tumor spread following all treatments.

Acknowledgements
The author is grateful to Dr Michael Baumann for critical review. He thanks Mrs Patricia Chick for preparation of the manuscript.

References


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