Causes of failure of radiotherapy in head and neck cancer

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Summary

Causes of failure of radiation therapy are reviewed and illustrated with clinical examples from cancers of the head and neck region. Radiobiological factors relating to volume of cancer, hypoxia, tumor cell kinetics, intrinsic cellular radiosensitivity and repair capability are considered, along with physical factors relating to fraction size and inadvertent underdosage. In addition, reference is made to failures attributable to a sigmoid dose response curve for tumor control and to the development of second primary cancers. The distinction is made between those causes of failure that can be minimized by optimal application of concepts and techniques readily available to all radiotherapists, those that are not amenable to any modification of radiotherapeutic technique, and those that are potentially remediable by new treatment strategies based on the radiobiological attributes of individual tumors.

Introduction

Analysis of causes of failure of radiotherapy serves two important functions. It suggests ways in which failures may be reduced by appropriate modification of radiotherapy technique, or when this is not possible, it delineates the circumstances under which radiotherapy should not be used for primary treatment. Cancers of the head and neck region lend themselves to accurate evaluation of the causes of failure because they are generally easier to stage and to follow than tumors in other sites of the body. However, the conclusion of analyses reached on the basis of head and neck cancer can be extrapolated to other anatomical sites. We will review causes of failure not only for definitive radiation therapy, but also for the widely used approach of combined treatment with surgery and post-operative radiation therapy.

Histology

For the first half of the century, radiosensitivity was considered to be a simple function of histology. Different histological tumor types were classified as radiosensitive, moderately radiosensitive, or radioresistant [17], and for the radioresistant tumors there was no need to look for causes of failure other than their histology. Furthermore, within the mod-
erately radiosensitive group, differences in radiosensitivity were attributed to anatomical location. For instance, squamous carcinoma of the mobile tongue was considered to be more radiosensitive than squamous carcinoma in the base of the tongue, or squamous carcinoma metastatic to cervical lymph nodes. This conclusion can be traced to the fact that higher doses of radiation could be delivered using interstitial techniques to the oral tongue compared with the limited doses that were feasible with external beam therapy using kilovoltage treatment machines.

Although it is undoubtedly true that tumors of certain histological types are more radiocurable than others, it is by no means established that this correlates with inherent differences in cellular radiosensitivity (see below), as opposed to epigenetic and environmental factors such as the proportion of tumor stem cells, tumor cell kinetics, and oxygen status. In fact, the available evidence suggests that histology per se is not a major determinant of radiocurability. This conclusion can be reached from the fact that the control of subclinical disease in various anatomical sites is essentially independent of histology [12]. An example from the head and neck region is provided in Table I which shows that for a variety of histological types of parotid cancer treated by surgery and postoperative irradiation, failures occurred with approximately equal frequency among the more malignant histotypes.

**Volume of cancer**

The probability of control of any cancer at a given dose level is a function of the number of clonogenic cells that need to be eliminated. It is not possible to measure directly the number of clonogenic cells in human tumors, but for different classes of tumors, it is reasonable to suppose that the clonogenic cell number is closely correlated with tumor volume. The influence of volume of cancer on the probability of control of cervical lymph node metastases from squamous carcinomas of the laryngopharynx is illustrated in Table II. These data show not only a decreasing control probability with increasing size of lymph nodes within each dose range, but also a dose dependence for control within each size range.

The principle of volume of cancer also has important application in the treatment of subclinical disease. The concept of subclinical disease as advanced by Fletcher [11] is precise and was applied to specific anatomical areas amenable to clinical examination. The two main applications were as follows: (1) Clinically negative lymphatic areas in

### Table I

Local-regional failures by histologic types after resection and postoperative irradiation.

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of patients</th>
<th>Failures</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Primary</td>
<td>Neck</td>
<td>Primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>site a</td>
<td>site</td>
<td>site and neck</td>
</tr>
<tr>
<td>Malignant mixed</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>17</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mucoepidermoid (low grade)</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucoepidermoid (high grade)</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Acinic cell</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

* Including the facial nerve into the base of the skull.


### Table II

Control rates as a function of the size of the node(s) and radiation dose in the squamous cell carcinomas of the laryngopharynx.

<table>
<thead>
<tr>
<th>Dose Size</th>
<th>Dose Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 cm</td>
<td>3-5 cm</td>
</tr>
<tr>
<td>≤65 Gy</td>
<td>15/26 (58%)</td>
</tr>
<tr>
<td>&gt;65 Gy</td>
<td>86/95 (91%)</td>
</tr>
</tbody>
</table>

* Determinate group.

From Bataini et al [4].
which a high probability of occult disease was known to exist: (2) areas rendered free of clinically detectable disease by limited surgical excision of a circumscribed tumor mass. In these situations it has been repeatedly substantiated that 50 Gy in 25 fractions over 5 weeks eradicates in excess of 95% of occult disease.

However, for conventional postoperative therapy the concept of subclinical disease is not directly applicable, and the dose of radiation required must be modified according to the density of infestation of the operative bed by tumor cells as deduced from the surgical pathology. Another consideration is that after extensive surgical dissections, residual tumor cells are more likely to be in a poorly vascularized environment. This can frequently be appreciated clinically by a lesser skin reaction and/or failure of epilation in a surgical flap when compared with adjacent undisturbed skin in the radiation field. For these reasons there is no single entity of subclinical disease in the postoperative setting, and the dose required must be based on the features of the individual case.

Tumor cell hypoxia

Over the past three decades, hypoxic cells have been considered the single most significant cause of treatment failure, and most new radiotherapy regimens are still predicated on this belief. Although the existence of hypoxic tumor cells is indisputable, the question of how frequently they determine treatment failure with optimum fractionated techniques is still the subject of controversy. The most direct evidence would be expected from trials of radiotherapy in hyperbaric oxygen versus ambient conditions, or from trials of selective hypoxic cell radiosensitizers. However, with very few exceptions, these trials have shown benefit only when a few high dose fraction treatment regimens have been employed [8]. This may be related to the greater influence of a biphasic survival curve when large dose fractions are used, and also to the probability that the oxygen enhancement ratio is lower with small doses per fraction where cell killing is mainly due to the single-hit or alpha-component [1]. Further support for this interpretation is obtained from the success of low dose rate interstitial techniques in the head and neck region.

Deficient reoxygenation is a potential cause of failure of fractionated treatment. However, it should be remembered that reoxygenation need not be complete when using fractionated treatment, and, in fact, with incremental doses of 200 cGy or less the influence of hypoxic cells would not be significant unless they constituted close to 50% of the viable tumor cell population at the time of each dose [26].

Tumor regeneration

Because of the relatively slow growth rate of most human tumors (median volume doubling time about 2 months) [6], tumor cell regeneration during a conventional course of fractionated treatment lasting 6–7 weeks has generally been discounted as a cause of failure. However, the critical parameter
TABLE III
Recurrences in the head and neck of patients electively irradiated postoperatively for Stages III and IV epidermoid carcinoma of the head and neck.

<table>
<thead>
<tr>
<th></th>
<th>Delay up to 6 wks</th>
<th>Delay over 6 wks*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>(%)</td>
</tr>
<tr>
<td>Nodes negative</td>
<td>0/5</td>
<td>0</td>
</tr>
<tr>
<td>Nodes positive at one level</td>
<td>0/18</td>
<td>0</td>
</tr>
<tr>
<td>Nodes positive at multiple levels</td>
<td>2/25</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>2/48</td>
<td>4</td>
</tr>
</tbody>
</table>

* In the patients with a delay over 6 weeks there was no palpable disease at the time of the initiation of irradiation.

From Vikram et al. [23].

is not the volume doubling time, but the potential doubling time of the clonogenic tumor cell population. The most direct evidence to implicate tumor cell regeneration as a cause of failure in head and neck cancer comes from the data of Parsons et al. [16]. These authors showed that when the same total dose in the same number of fractions was given as either a continuous or split course, local control was superior in all stages for the continuous treatment. This implies that regeneration occurring during the 2 weeks gap in the split course regimen contributed to tumor failure.

The rapid rate of proliferation of tumor cells surviving unsuccessful radiotherapy is attested to by the fact that the great majority of failures in head and neck cancer are manifest within 2 years of treatment regardless of tumor growth rate prior to treatment (Fig. 1). Furthermore, delay between surgery and the initiation of postoperative radiotherapy has been shown to have a major influence on the success of the combined treatment with a delay of 6 weeks or more being associated with a much higher relapse rate than with shorter time intervals (Table III).

In certain circumstances, even the continuous administration of 10 Gy per week may not be sufficient to counter tumor regeneration. For example, it is not uncommon for neck metastasis to grow during treatment and occasionally patients who had no palpable disease at the initiation of postoperative irradiation can develop overt disease during treatment (Fig. 2). In these circumstances accelerated fractionation in the form of a concomitant boost is indicated [22].

Failures of redistribution

Failure of redistribution is another potential cause of failure of conventional fractionated treatment. It is well documented that significant variations in cellular radiosensitivity exist as a function of cell age in the division cycle. In fact, with small incremental doses the magnitude of differences in radiosensitivity attributable to the cell age can exceed that imposed by tumor cell hypoxia [20]. It follows that tumors having a large non-growth fraction of clonogenic cells would therefore be relatively resistant to conventional fractionated treatment because of nonprogression of cells from more resistant phases of the division cycle.

A long tumor cell turnover time is also correlated with a slow volume regression after commencement of radiotherapy, and it is possible that failure of redistribution could account for the clinical observation that tumors which do not "clear" completely during a course of treatment are less likely to be cured [3]. However, other factors, such as failure of reoxygenation cannot be excluded. Since variation in radiosensitivity with cell age is much less with high LET radiations, it was predicted [25] that the RBE of tumors that redistributed poorly would be high, providing a "kinetic gain factor" for neutron therapy. Limited clinical confirmation of this prediction has been provided by studies on lung metastases with widely varying growth rates [5] and kinetic analysis of tumors to select tumors with a low turnover rate for trials of high LET irradiations would appear rational and justified.
Fig. 2. Patient was referred in June 1979 for postoperative irradiation after extensive surgery for a squamous cell carcinoma of the ear. At the start of irradiation there was no palpable disease in the entire area. Approximately one week after the start of irradiation at 10 Gy/week, a suspicious area was palpated in the supraclavicular area; by the second week it was definite. Through a small field within the large field 5 × 200 cGy was added in one week (A). The second treatment was given as a concomitant boost 3 h after the first one. At the completion of treatment there was moist desquamation of the skin in the field-within-the-field area (B). The total dose to the nodule was 66 Gy in 5 weeks. The tumor had clinically disappeared and the patient was NED in May 1982. From Fletcher [14].

**Intrinsic cellular radiosensitivity and repair capability**

Although no direct evidence can be adduced to show that the intrinsic cellular radiosensitivity and/or repair capability of tumor cells is a major cause of failure in the treatment of human cancer, radiobiological data suggest that this is likely to be the case. Significant differences in the initial slope and shape of the shoulder of the survival curve of various human tumor cell lines have been demonstrated [9] and relatively small differences in cell survival after low doses would have an enormous effect on the success of a fractionated course of treatment due to the amplification of the fractionation process. For example, the difference between a surviving fraction of 60% or 50% after an incremental dose of 200 cGy would lead to a difference of 2.8 logs of cell killing in a fractionated course of 70 Gy, assuming equal effect per fraction.

However, the true magnitude of differences in survival fraction after each dose may not be represented in classical cell survival experiments. Weichselbaum and Little [24] have recently reviewed the differences in capacity to repair potentially lethal damage between various cell lines derived from human tumors. These authors make the case that such differences may be more important than classical cell survival in determining the outcome of treatment. This area is clearly one deserving of research emphasis, especially with regard to measurements on fresh human tumor explants.
Fraction size

Extensive clinical experience supports the observation that use of large fractional doses changes the proportionality between acute and late normal tissue reactions with a relative increase in severity of late reactions [22]. Insofar as tumors can be regarded kinetically as more resembling acutely reacting normal tissues than late reacting ones, it can be argued that use of small incremental dose fractions will increase the therapeutic ratio between tumor control and late normal tissue injury. This is the rationale for hyperfractionation. Using the same argument, one would predict that the use of larger dose fractions would be associated with a poorer therapeutic ratio. This prediction is supported by the analysis of results by Cox et al. [7] showing that hypofractionated regimens with the same NSD were associated with poorer local disease control than conventional fractionation schemes. However, conflicting results have been reported by Henk [15] who observed no difference in disease control in a randomized trial using 30 or 10 fractions for definitive treatment of head and neck cancer.

Sigmoid dose-response curve

As a consequence of the randomness of cell killing by radiation, the probability of curing any tumor is determined by Poisson statistics and is a sigmoid function of dose. Up to a certain dose the tumor control probability is small, following which there is a steep increase with increasing dose until a pla-
teau is reached in which a large additional dose is necessary to achieve a relatively small increase in tumor control probability. A great deal of spurious argument exists in the literature concerning the presence or absence of dose-response curves for the control of head and neck cancers. Unless one postulates that there are subpopulations of tumor cells which are absolutely resistant to radiation (which has never been observed), it is impossible to escape the conclusion that tumor control probability is a Poisson function of dose. The problem of demonstrating dose-response relationships in clinical material is attributable to the following factors:

1. Human tumors, even within the same stage category, are heterogeneous with regard to all of the features determining radiocurability. Such heterogeneity inevitably acts to flatten the dose-response relationship [19].

2. Patients have been randomly assigned to receive different dose levels in very few clinical studies. Thus, the bias exists to give higher doses to patients with more advanced disease which again will tend to flatten the dose-response function.

3. Rarely are doses calculated at the site of tumor failure and this can differ significantly from the prescribed tumor dose.

4. With few exceptions, no quality assurance can be obtained that technical errors did not contribute randomly to causes of failure.

In spite of these limitations, at least some clinical dose-response analyses show significant positive slopes (Fig. 3). Even with steep curves, however, there is a point beyond which the likelihood of improving the therapeutic ratio is small. The more heterogeneous the population the lower the tumor control probability at which this plateau is reached.

**Inadvertent or underdosage**

The surest cause of radiotherapy failure is the geographic miss or inadvertent underdosage. This factor must always be excluded in any analysis of dose-response relationships for radiotherapy. Although flagrant and obvious geographic misses still unfortunately occur, we will focus here on subtle and sometimes unappreciated examples of underdosage. Examples from the head and neck region include the following.

**Off-axis dosimetry.** Inadvertent underdosage may account for the cause of failure of at least 10% of cancers of the nasopharynx. This is because the primary tumor is located in the corner of the radiation field and the actual dose received is significantly less than the calculated central axis dose because the isodose curves are not flat to the geometric edges of the beam. Although less significant than with kilovoltage irradiation, differential bone absorption

![Fig. 4. Isodose distribution, with two dimensional corrections for tissue inhomogeneities for a direct anterior 17 MeV electron beam field to the nose. Doses along the beam axis are significantly lower than in a homogeneous phantom (e.g. at the expected 90% depth of 5.2 cm, the dose is in fact 64%). On the other hand, serious hot spots exist off the beam axis. From Fields and Hogstrom [10].](image-url)
TABLE IV


<table>
<thead>
<tr>
<th>Stage</th>
<th>Total</th>
<th>Primary failure</th>
<th>Definite ultimate failure after surgical salvage</th>
<th>Underdose or geographic miss</th>
<th>NED 2 yrs</th>
<th>NED locally expired 2 yrs other causes (DM, ID, UNK)</th>
<th>Analyzed case</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>26</td>
<td>15% (4/26)</td>
<td>4% (1/26)</td>
<td>2</td>
<td>18</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>T2</td>
<td>103</td>
<td>19% (20/103)</td>
<td>7% (7/103)</td>
<td>5</td>
<td>66</td>
<td>17</td>
<td>81</td>
</tr>
<tr>
<td>T3</td>
<td>61</td>
<td>15% (9/61)</td>
<td>3% (2/61)</td>
<td>5</td>
<td>36</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>T4</td>
<td>14</td>
<td>36% (5/14)</td>
<td>21% (3/14)</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: DM = distant metastases; ID = intercurrent disease; UNK = unknown cause; NED = no evidence of disease. From Barker and Fletcher [2].

also contributes a little to the underdosage of the primary tumor. An analysis of nasopharyngeal tumors treated at U.T. M.D.A.H. from 1954 to 1971 with a nominal 60 Gy tumor dose for T2 squamous cell carcinomas showed a significant incidence of failure at the primary site (12/43). Subsequent to 1972, a small field centered over the angle of the nasopharynx was used to deliver an extra dose of 500–750 cGy, and this reduced the incidence of failure of T2 squamous cell carcinoma to 1/14 [13]. This cause of failure by underdosage was not evident with the lymphoepitheliomas since lower doses are required for the same tumor control probability as with “pure” squamous cell carcinoma.

Skin sparing. The increasing use of high energy photons for head and neck cancer has led to the risk of inappropriate skin sparing, especially in the postoperative setting. In general, photon energies in excess of 4 MeV or 60Co are unwise when the neck is being treated postoperatively. A related but less well known effect is the build-down phenomenon. This refers to the reduction of dose at a tissue-air interface as a photon beam exits the tissue due to lack of backscatter. Thus large cavities, for example after a radial maxillectomy, should be treated with the obturator in place or other suitable bolus.

Treatment with electrons or a mixture of electrons and high energy photons. Electron beams are subject to a much greater risk of inadvertent underdosage than photons. This is because of the greater perturbation introduced by tissue inhomogeneities, and the possibility of a geographic miss in depth. Figure 4 shows the isodose distribution obtained from a direct anterior electron beam field to the region of the nose with correction for tissue inhomogeneity. It is readily apparent that a major underdosage can result if these corrections are not made. Figure 4 also shows that significant hot spots can coexist with tumor underdosage if simple uncompensated electron beam portals are used. Another dosimetric problem shared by electron and high energy photon beams is forward peaking of the isodose curves to a much greater extent than that associated with 4–6 MeV X-rays or well-trimmed 60Co beams. This is illustrated by an analysis of failures in squamous cell carcinomas of the retromolar trigone-anterior faucial pillar treated at U.T. M.D.A.H. Table IV shows that the failure rate is about the same as one progresses from T1 to T3 on
linear dimensions reflecting the small change in volume of cancer. However, in all stages most failures occurred anteriorly. Analysis showed that patients treated with parallel opposed $^{60}$Co fields with equal or 2:1 loading had fewer failures than those treated with ipsilateral high energy electron beams alone or in combination with high energy photons. In retrospect, this can be ascribed to the significant forward peaking of the isodose curves of these beams. Lesions of the retromolar trigone-anterior faucial pillar often do not have a clear delineation, being surrounded by areas of leukoplakia along the buccal mucosa and lower gum. Thus, microscopic disease anteriorly is easily underdosed. Subsequent to the analysis of Table IV, the use of a generous anterior margin has significantly diminished the incidence of failures in this location.

### Second primary cancers

Apparent failure of radiotherapy can result from the development of a second primary cancer within or adjacent to the previously treated area. This is particularly relevant to the head and neck region, since the habits contributing to the development of cancers are usually perpetrated by this patient population. In some circumstances, it is difficult to distinguish between a marginal recurrence due to inadequate coverage, as described above in relation to cancer of the retromolar trigone-anterior faucial pillar, and genuine second primary cancers occurring within the irradiated volume. However, a long time to “recurrence” after apparently successful treatment points toward the development of a new primary lesion. The data in Table V illustrate the point with regard to cancers of the larynx. Whereas most failures in the supraglottic larynx were manifest within 2 years, and all within 3 years (Fig. 1), apparent recurrences of glottic cancer continued to occur for 7–10 years, frequently on the contralateral cord, strongly suggesting that these late recurrences were indeed second primaries.

### Discussion

Cancers of the head and neck region provide good illustrations of many of the potential causes of failure of radiotherapy. Awareness of the various fac-

### TABLE V

Cumulative appearance of failures for borderline histology lesions of the vocal cords compared with those for invasive squamous cell carcinomas of the vocal cords and supraglottic larynx – 1952 through 1973 (analysis, July 1975).

<table>
<thead>
<tr>
<th></th>
<th>No. failures/No. patients</th>
<th>Time after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 yr</td>
</tr>
<tr>
<td>$T_1 + T_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocal cords</td>
<td>12/86</td>
<td>0%</td>
</tr>
<tr>
<td>(in situ)</td>
<td>(0/12)</td>
<td>(3/12)</td>
</tr>
<tr>
<td>$T_1 + T_2$</td>
<td></td>
<td>41.5%</td>
</tr>
<tr>
<td>Vocal cords</td>
<td>65/330</td>
<td>(27/65)</td>
</tr>
<tr>
<td>(invasive carcinoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_1 + T_2$</td>
<td></td>
<td>66.5%</td>
</tr>
<tr>
<td>Supraglottic larynx</td>
<td>15/96</td>
<td>(10/15)</td>
</tr>
<tr>
<td>(squamous cell)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Pene and Fletcher [18].
tors that may contribute to treatment failure is essential when one plans new therapeutic strategies. For too long, radiotherapists have been so obsessed with the oxygen effect that other factors of equal or greater importance have been ignored. This is not to say that oxygen is unimportant, but it must be put into perspective.

Many of the potential causes of failure are easily remediable with existing concepts and technology. For example, inadvertent underdosage and geographic misses should rarely occur if radiotherapists are alert to the circumstances when underdosage is a risk, and adequate quality control is maintained. Similarly, concepts such as titration of radiation dose to the volume of cancer present, avoidance of split courses that unduly protract the duration of treatment or unnecessary delay between surgery and postoperative irradiation, and the use of concomitant boosts when there is evidence of rapid tumor growth are simple to understand and easy to apply in clinical practice.

On the other hand, there are some causes of failure, e.g. the development of second primaries, and recurrences due to the randomness of radiation cell killing that cannot be overcome by any modification of radiotherapeutic technique. There remains, however, a significant proportion of tumors that cannot be controlled with optimal existing techniques, in which the cause of failure is potentially remediable. Radiotherapists have a variety of new strategies in their armamentarium, but up till now, these have generally been tested in an unselective way on all “resistant” tumors. When a new strategy is aimed at only one or two potential causes of failure, it is obvious that the chances of demonstrating a benefit for the subset of patients who might be helped are diluted by the inclusion of patients whose cause of failure is unrelated to the rationale of the new treatment strategy. The hope and challenge for the future is that better means of identifying and monitoring potential causes of treatment failure will be developed so that eventually the therapeutic regimen recommended for a given patient will be determined by the characteristics of his particular tumor.

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References
