The Hydra Phenomenon of Cancer: Why Tumors Recur Locally after Microscopically Complete Resection

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Abstract
After surgical resection with microscopically clear margins, solid malignant tumors recur locally in up to 50%. Although the effect of a local tumor recurrence on the overall survival may be low in common cancers such as carcinoma of the breast or prostate, the affected patients suffer from exacerbated fear and the burden of the secondary treatment. With some tumor entities such as carcinoma of the uterine cervix or carcinoma of the head and neck, a local recurrence indicates incurability in the majority of cases. The pathomechanisms of local tumor spread and relapse formation are still unclear and comparatively little research has been devoted to their elucidation. Through the analysis of clinical and molecular data, we propose the concept of two pathogenetically and prognostically different local relapse types (i) in situ recurrences that arise in the residual organ/system not involved in the surgery for the primary tumor and (ii) scar recurrences that develop at the site of previous tumor resection. Whereas field cancerization, the monoclonal or multiclonal displacement of normal epithelium by a genetically altered but microscopically indistinguishable homologue, may explain the origin of in situ recurrences, most scar recurrences are regarded as the result of the interaction of minimal residual microscopically occult cancer with the surgical wound environment inside a developmentally defined tissue or organ compartment. The therapeutic implications derived from these concepts and areas of future research aimed to reduce local relapses are discussed in this perspective. (Cancer Res 2005; 65(8); 2997-3002)

Clinical Problem of Local Recurrences after Surgical Resection

According to the current WHO world cancer report, cancer continues to be the second most important cause of death in developed countries killing 23% of their population (1). With many common cancers such as carcinoma of the breast and prostate, mortality from malignant disease is mainly due to the formation of metastases, and much effort is currently spent on investigating distant cancer dissemination. However, with some tumor entities such as cancer of the uterine cervix or carcinoma of the head and neck a considerable number of patients die from uncontrolled primary and recurrent local disease. Even if the effect on overall survival may be low, the occurrence of local tumor relapse increases anxiety and the burden of treatment in the affected patient. Yet, research addressing the pathomechanisms of local tumor spread and local relapse formation has been comparably sparse.

Most solid malignant neoplasms are treated with surgical resection for local control and microscopically negative surgical margins after tumor removal (R0 resection) are crucial for the prevention of local recurrence. Nevertheless, local recurrence rates after wide surgical resection with microscopically clear margins range between 5% and 50% without adjuvant treatment (Table 1). (Neo)adjuvant radiation or chemoradiation may decrease the probability of local recurrences after surgical resection and is therefore part of a patient’s individual treatment plan if the tumor exhibits specific histologic high risk factors. However, additional morbidity may result from multimodal local treatment.

Classification of Post-Surgical Local Relapses

Local recurrences develop at the site of the primary surgery/surgical scar (scar recurrences) or at some distance from this location in the residual organ that remained in situ after resection (in situ recurrences: Fig. 1). Discrimination between these two types of local recurrences is important as their different prognosis points to differences in their pathogenesis. A much inferior outcome for patients with scar recurrences compared with in situ recurrences has been shown with breast and vulvar cancer (2–4).

The pathogenesis of in situ recurrences can be explained by the phenomenon of field cancerization. To understand the pathogenesis of scar recurrences after microscopically complete tumor resection (R0), we need to look at the mechanisms of local tumor spread and the interaction of minimal residual cancer with the surgical wound.

Field Cancerization

First proposed for oral cancer by Slaughter et al. (5), field cancerization describes clinically occult multifocal preneoplastic lesions of the epithelium within an anatomic region exposed to the same carcinogen(s) [e.g., cigarette smoking, human papillomavirus (HPV) infection]. These lesions may not be apparent at histopathologic investigation but can be detected with molecular analyses for phenotypic or genetic alterations associated with carcinogenesis such as p53 gene mutations, integrated viral DNA, loss of heterozygosity, and microsatellite instability. Field cancerization has been described for lung, esophagus, vulva, cervix, anus, colon, breast, bladder, and skin in addition to the oral cavity, pharynx, and larynx (6, 7).

Both, monoclonal and polyclonal lesions have been shown in those fields with genetically altered cells by X chromosome inactivation analysis and comparison of distinct gene mutations. Polyclonality is explained by multiple genetic lesions produced independently from each other by the same carcinogenic local environment. Monoclonal fields result from the lateral expansion of a “patch” formed by a genetically altered stem cell exhibiting a significant growth advantage over the neighboring stem cells. Cohesive lateral migration of these cells gradually displaces the normal epithelium.
After the complete resection of a carcinoma preserving part of the organ in which it developed, microscopically normal but genetically altered epithelium may remain in situ and acquire additional mutations or epigenetic alterations that can initiate the development of a second tumor of the same or a different histologic type, representing an in situ recurrence. If the resection margin of the tumor operation is located within this genetically altered epithelium, a scar recurrence could also be a consequence of field cancerization (Fig. 1). However, the pathomechanism involving minimal residual cancer that will be described below seems to be more frequent (8).

Mechanisms of Local Tumor Spread

Local spread of a solid malignant tumor can be followed at three levels of magnitude: macroscopic/microscopic/occult. Occult tumor spread can be traced with PCR-based molecular probes for specific tumor cell–derived DNA and RNA sequences. Alternatively, occult tumor cells may be highlighted by immunocytochemistry albeit with a much lower detection rate. At present, only a few studies have assessed occult local tumor propagation whereas numerous investigations have been devoted to the detection of regional and systemic minimal residual disease (9). By identifying p53 mutations in individual head and neck cancers, Brennan et al. showed the presence of tumor cells at the surgical resection margins microscopically free of disease in 50% of the cases (10). Similar findings were recently reported for non–small cell lung cancer (11).

As many carcinomas of the uterine cervix harbor integrated HPV 16 and 18 sequences in their DNA, the sequence information of the 5’ and 3’ viral-cellular junction loci can be used as the basis for individual PCR assays to detect microscopically occult cervical cancer (12). We have applied integrate-specific PCR in specimens of anatomically precisely defined locations remote from the tumor border in patients with cervical carcinoma treated surgically. Whereas a low background of cancer DNA was found in nearly all investigated pelvic and extrapelvic locations, most probably as a consequence of hematogenous, lymphatic and i.p. tumor cell dissemination, significantly more often tumor DNA was identified within an anatomic compartment comprised of the cervix, proximal vagina, and their posterolateral supply and support structures with a higher probability closer to the microscopic tumor border than remote from it (13). This cervicovaginal compartment can be regarded as the adult morphogenetic unit arising in the female individual from the distant segment of the bilateral paramesonephric (Mullerian) ducts under the influence of the HOXA-13 gene (14). From magnetic resonance imaging studies,

Table 1. Local recurrence rates (LRR) of selected tumor entities after surgical treatment with microscopically clear margins (R0) without adjuvant radiation

<table>
<thead>
<tr>
<th>Tumor entity</th>
<th>LRR (%)</th>
<th>Remarks</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck carcinoma</td>
<td>4-50</td>
<td>Regional recurrences included</td>
<td>(33, 10)</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>6-19</td>
<td>After breast conserving surgery</td>
<td>(36, 37)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>22-39</td>
<td>Regional recurrences included</td>
<td>(38, 39)</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>20-33</td>
<td></td>
<td>(40, 41)</td>
</tr>
<tr>
<td>Rectal carcinoma</td>
<td>10-27</td>
<td>Regional recurrences included</td>
<td>(42, 43)</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>10-25</td>
<td>Regional recurrences included</td>
<td>(44, 45)</td>
</tr>
<tr>
<td>Vulvar carcinoma</td>
<td>16-19</td>
<td></td>
<td>(46, 47)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>8-36</td>
<td></td>
<td>(48)</td>
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the histopathologic investigation of surgical specimens and molecular mapping local cervical cancer spread can be located within the cervicovaginal compartment over a long time in malignant progression. Only late in that process, the uterine corpus and the adjacent visceral compartments such as the bladder compartment anteriorly and rectum compartment posteriorly may be invaded by the tumor, although these tissues are just a few millimeters apart from the site of tumor origin and no fascia or condensed fibrous tissue layer separates them. The observation that tumor cells migrate and proliferate within a developmentally defined tissue or organ compartment is the same in vulvar, endometrium, ovarian, and colorectal carcinoma and could be a general principle. What makes local tumor spread remain confined to the morphogenetic unit for a relatively long period of time?

Local tumor spread takes place by the collective migration of cancer cells or by migrating individual tumor cells (15). There is evidence that individual migrating cancer cells separate from the cell collective by epithelial-mesenchymal transition (EMT), a highly conserved process of morphogenesis in multicellular organisms (15, 16). The loss of the epithelial phenotype in the cancer cell often is a consequence of E-cadherin lack of function that may result from mutation or more frequently from epigenetic down-regulation through transcription repression or promoter hypermethylation (16). Several transcriptional repressors of E-cadherin such as snail, slug, and snip 1 have been found to be expressed with morphogenetic processes in the embryo as well as in highly invasive cancer cell lines. An important upstream signaling mechanism is the binding of hepatocyte growth factor (scatter factor) to the Met receptor. Overexpression of Met in cancer cells can be induced by hypoxic conditions and may represent a clinically significant event in hypoxia-associated tumor progression and invasion (17, 18).

Similar signaling mechanisms resulting in E-cadherin down-regulation and EMT are activated by the binding of semaphorins to their receptors (plexins) both of which are structurally related to Met (19). Likewise, binding of several other structurally unrelated growth factors to their ligands including insulin-like growth factor (IGF), epithelial cell growth factor, and the ErbB family, fibroblast growth factors and transforming growth factor-β (TGFβ) may induce EMT. These cascades also orchestrate other molecular mechanisms essential for cell migration, particularly the synthesis, affinity, and avidity of integrins and the activity of matrix metalloproteinases (MMP). Integrins form the contacts to the extracellular matrix (ECM) and MMPs focally degrade and remodel ECM during cell migration. These processes are interrelated by the integrins’ ability to mediate cellular inside-out and outside-in signaling and to activate and localize MMPs (20).

We hypothesize that migrating tumor cells, either individual or as members of a moving collective, respect positional information of the local environment until late in malignant progression. Their migration, survival, and proliferation is actively guided by tissue-specific contacts and signals rather than following paths of low mechanical resistance. Positional information is generated by the gene expression of the local fibroblasts, blood, and lymphatic vessels and is presented through the corresponding ECM and various molecular signals (21, 22). Homologous positional information is retained in adult anatomic structures derived from a common precursor tissue (anlage) during embryologic and fetal development defining a morphogenetic unit. The integrin expression on the surface of the migrating tumor cells may fit to the compartment-specific ECM ligands preventing integrin-mediated apoptosis (23). Tumor cell migration initiated within the tumor microenvironment by the various molecular mechanisms described above may be maintained beyond the tumor border by compartment specific promigratory signals, such as local semaphorins and plexins (19). Only late in malignant progression when tumor cells have gained migrational plasticity (15) and apoptotic resistance (24), these permissive effects of the compartment specific environment are no longer relevant for local tumor propagation.

Interaction between Minimal Residual Cancer and Surgical Wounds

The interaction of occult tumor cells and surgical wounds may happen locally at the site of tumor resection as well as remote from it at the sites of surgical access to the body cavities or compartments. If the migration of tumor cells detached from the primary neoplasm is guided by positional information expressed within the developmentally defined morphogenetic unit, then the probability of occult tumor cells being present within or close to the local surgical wound created during the process of tumor resection should be much higher than the probability of their presence in remote wounds. Moreover, wound-associated activated blood vessels within the compartment may favor a reentry of circulating tumor (stem) cells into the compartment further increasing the probability of minimal residual disease within the local wounds (25). Even lymphatic and hematogenous tumor cell dissemination as well as contamination will probably contribute to a higher load of minimal residual disease at the site of the local compared with the remote surgically produced tissue injury due to dilution effects. Consequently, recurrences in the local surgical scar area should be found much more often than remote scar recurrences that certainly reflects the clinical experience. Recurrences after tumor resection with microscopically free margins (R0) occur locally at the site of surgical resection in up to 50%, whereas recurrences in the distant surgical scar are reported in only 1% to 2% (26). Once exposed to the wound environment, neoplastic cells receive various stimuli and experience conditions favoring the formation of a tumor relapse. Table 2 gives a survey of proposed mechanisms of the interaction between minimal residual cancer and the surgical wound. Depending on the different phases of the healing process cancer cells may be recruited, replicated, and selected at the site of the surgical wound (27–31).

Although the local immunomodulating effects of the surgical wound during the different phases of healing may be complex, the established systemic immunosuppressive consequences of surgery should support the relapse formation. It can be assumed that most of the wound-associated tumor promoting effects are related to the wound volume, especially to the extent of ischemia within a wound. Secondary healing wounds should therefore be more prone to support scar recurrence formation than wounds healing per primam.

Therapeutic Implications

Following the arguments of the preceding chapters the current principles of surgical oncology have to be revisited. A radical tumor operation must remove not only the macroscopic and microscopic tumor but also a maximum of the microscopically occult local cancer with a minimum of tissue trauma. The corresponding surgical anatomy has to be deduced from embryologic and fetal development defining the morphogenetic units in the adult. Conventional radical tumor operations based on the Halsted...
principles may not adequately address these criteria being too traumatic due to unnecessary removal of tissue not infiltrated by occult cancer on one hand and not sufficiently radical with respect to the eradication of occult local cancer on the other hand (Fig. 1).

Both, total mesorectal excision for rectal cancer and total mesometrial resection for cervical cancer are successful examples of the new concept of radical operations based on surgical anatomy from the developmental perspective (32, 33). The surgical treatment alternative for a radical tumor operation as defined above is a wide excision, again with minimal trauma, supplemented by adjuvant (chemo)radiation in the presence of high risk factors. The treatment yielding the best therapeutic index should be chosen for the individual patient.

With respect to the concepts introduced herein the design of radiation fields for adjuvant radiotherapy may have to be modified as well. Complex geometric target volumes addressing the topography of the morphogenetic units can be generated with the new technology of intensity modulated radiation therapy and tailored for the individual patient.

In case of an insufficiently radical primary operation, serious considerations should be given to the indication of reoperations with the goal to resect the perifocal scar tissue (34) eventually along with remnants of the corresponding morphogenetic unit.

Future Research

The investigation of gene expression profiles associated with the positional identity of cells may open an exciting new field, molecular topographical anatomy. Do mesenchymal cells of a morphogenetic unit that represents the adult anatomic compartment resulting from a certain anlage share a common topographical differentiation fixed in a defined gene expression profile as a positional memory? Can it be discriminated from the transcriptional pattern of corresponding cells from adjacent compartments? The transcriptome characterizing the topographical identity of fibroblasts may be reduced to the “HOX code” according to the suggestion of Chang et al. (21). Based on the HOX code of fibroblasts a topographical mapping of tissues may be deduced which might be important for the prediction of local tumor spread.

The identification of those molecular substrates guiding tumor cell migration within the permissive environment would be the next step. As the permissive environment for local tumor propagation seems to be topographically confined to the morphogenetic unit for a relatively long period in malignant progression a response of cancer cells to positional information presented by the mesenchymal cells of this compartment can be expected.

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**Table 2. Proposed mechanism of interaction between minimal residual cancer and the surgical wound at the site of tumor resection**

<table>
<thead>
<tr>
<th>Coagulation Phase</th>
<th>Inflammation Phase</th>
<th>Proliferation Phase</th>
<th>Remodelling Phase</th>
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<tbody>
<tr>
<td>Tumor cells may be trapped within the initial provisional wound matrix and correlated substrates.</td>
<td>Chemoattractants and promigratory factors may direct adjacent cancer cells to the wound. Cancer cells have been shown to express receptors for inflammatory chemoattractant cytokines (“chemokines”) of at least two of the four major groups, CXC and CC, e.g., CXCR2, CXCR4, CCR3, CCR4, CCR5, CCR7, CCR10 (27). Various extracellular matrix degradation products and growth factors of the wound medium strongly attract tumor cells as well.</td>
<td>After concentration of the migrating single tumor cells the wound environment may activate their mesenchymal epithelial transition (MET) programme to form a collective.</td>
<td>Survival and growth factors suggest the survival and proliferation of the tumor cells. Neo-angiogenesis and experimental tumor growth has been stimulated with TGF-β, BGF, EGF, PDGF, IL-1, IL-6 and other cytokines of the wound environment. The wound associated mitogenic effects on minimal residual cancer can be exerted both in paracrine and endocrine manner (29, 29).</td>
</tr>
<tr>
<td>Wound hypoxia initially due to ischemia and later as a consequence of the proliferation burst may act as selection pressure for genetically and phenotypically heterogeneous occult tumor cells. Phenotypes which are apoptosis resistant, highly angiogenic, glycolytic or motile may gain growth advantages within a hypoxic wound microenvironment. The wound itself may increase DNA damage in genetically instable tumor cells by various mechanisms including the generation of reactive oxygen species, inhibition of p53 activity, cytochrome p450 or glutathione S-transferase isoenzymes by inflammatory cytokines resulting in an increase of cancer cell variants (31).</td>
<td>Wound-associated angiogenesis will promote local tumor formation (30).</td>
<td></td>
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Cancer Res 2005; 65: (8). April 15, 2005 3000 www.aacrjournals.org
Whereas much work has been devoted to the detection of minimal residual disease with regard to the prediction and prevention of metastases, research on local occult cancer spread has been sparse. With advanced biotechnology, molecular probes to highlight microscopically occult cancer are available now for a variety of solid malignancies. The main questions that should be addressed are the following: What is the exact topographical distribution of occult cancer cells adjacent to the macroscopic tumor mass and its microscopical border with respect to the site of tumor origin, margins, and tissues remaining in situ? What is the prognostic significance of local minimal residual disease? Is molecular staging of the resection margins appropriate for the indication of additional local treatment (resection or adjuvant radiation)?

Understanding the multifaceted interactions between surgical wounds and minimal residual disease at the site of tumor resection seems to be particularly rewarding as the wound is a topographically and histologically defined environment suitable for various strategies of therapeutic intervention with the goal to erase a minimal tumor load. Of course, all strategies of wound-directed antitumor treatment have to respect side effects caused by their interference with healing in terms of restoration of tissue integrity and tensile strength.

In summary, with this perspective we want to alert researchers to the clinical importance of local relapse formation after seemingly adequate surgical treatment (i.e., resection with clear margins). In the light of recent clinical and molecular data, the picture seems much more intricate than its mechanistic perception assuming that local tumor spread follows spaces of least mechanical resistance and that local recurrences are simply due to undetected macroscopic or microscopic tumor left behind after surgical treatment. We propose that local tumor spread is guided by positional information presented molecularly in the developmentally defined surgical anatomy. Microscopically occult minimal residual cancer recruited, expanded and selected by an ischemic surgical wound could be an important but potentially avoidable cause of local recurrence. Research focused on the mechanisms of local cancer spread and the interaction of cancer cells with the wound environment may translate into significant clinical progress.

Acknowledgments

Received 10/27/2004; revised 1/17/2005; accepted 2/1/2005.

Grant support: Fresenius-Kabi Deutschland GmbH (M. Höckel) and Else Kröner-Fresenius-Foundation (N. Doehrmann). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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