PATHOLOGICA 2020;112:229-233;
DOI: 10.32074/1591-951X-111

Historical Pathologica

Invasion and metastasis: a historical perspective

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Summary

The idea that neoplasms grow, becoming unresectable through dissemination, which is initially loco-regional, and systemic only in a later stage, is historically at the basis of the radical surgery – where, by 'radical', the old surgery meant the complete removal of the tumor and, in practice, aggressive surgery. Halsted's "radical mastectomy", as well as many principles of surgical anatomy of the first decades of the twentieth century, obey to an idea of tumor progression as a linear process taking place in continuity and contiguity, where the various anatomical layers and the peritumoral desmoplastic reaction are mistaken for a wall of defense against the neoplasm's dissemination, capable of containing and orienting it. However, the investigations of the processes of invasion and metastasis by Rudolf Virchow and Stephel Paget helped to reorient surgical approaches.

Introduction

Although the term "metastasis" (from the greek **μετάστασις** from **μετα-ἵστημι**, meaning a shift, a migration) was conceived a long time ago, in 1829, by Joseph Claude Anthelme Recaimier (1774-1852) [1], what exactly lies behind metastatic processes has been the subject of much debate ever since. Nowadays, there is hardly a review focusing on the processes of invasion and metastasis that fails to mention the so-called *seed and soil* hypothesis, attributed to the English surgeon Stephen Paget (1855-1926). In 1889, Paget published a report entitled "*Distribution of secondary growths in cancer of the breast*" [2], putting into print the rational explanation for the concept that metastatic cells interact with a specific organ micro-environment, which may either facilitate or obstruct the growth of secondary neoplasms. Paget's often-quoted question, "*What is it that decides what organ shall suffer in a case of disseminated cancer?*" formed the basis of his investigations [2] and Paget concluded that "*remote organs cannot be altogether passive or indifferent regarding embolism*". In a 1911 issue of *Pathologica* [3], in the introduction to an article entitled "*On a cancerous metastasis in a hepatic cavernoma*", F. Nassetti (at the Institute of Anatomia Patologica of the Royal University in Rome) wrote in a similar vein: "*The question of metastases is still obscure in many of its aspects. We do not know, for example, why tumors of certain organs (like the breast, thyroid, and prostate) frequently metastasize to the bone system, or why various organs in which a primary tumor easily develops (like the uterus, breast, or stomach) are vice versa scarcely receptive to metastatic formations*".

Received: April 9, 2020
Accepted: July 22, 2020

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Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Patriarca C, Pini GM, Conti G. Invasion and metastasis: a historical perspective. Pathologica 2020;112:229-233. https://doi.org/10.32074/1591-951X-111

Stephen Paget's observations were based on more than 700 autopsy reports on patients who had breast carcinomas associated with a high incidence of liver, ovary and specific bone metastases, and a low incidence of spleen metastases. They were subsequently questioned, nevertheless, by James Ewing (1866-1943), who envisaged a mechanism of metastatic discrimination as being mediated by purely mechanical forces and circulatory patterns [4]. This latter view, that a metastasis could be seen as the result of tumor cell emboli becoming lodged in an excessively narrow vasculature, coincided with Rudolf Virchow's (1821-1902)

Figure 1. Stephen Paget (1855-1926).

original interpretation, which largely explains why the view taken by Ewing came to prevail in the literature for decades. Dr. Paget's seminal paper went virtually unnoticed during his lifetime, joining the ranks of all those important discoveries whose authors were not taken seriously (another example is the scientific discovery of Enrico Sertoli (1842-1910), recently described in *Pathologica*) [5]. To quote Isaiah Fidler: "There are few scientists whose work will withstand 120 years of scrutiny or not succumb to the depressing trend of modern publications to ignore papers published more than 5 years ago" [6]. With time, however, the view taken by Stephen Paget was "completely vindicated" [6] and came to prevail in the 1970s and 1980s. Since then, it has been enriched over the decades with a profusion of new data and histological characterizations, and sustained more and more by a huge amount of information from molecular investigations (Fig. 1).

Invasion more than metastasis

In actual fact, the idea that neoplasms grow, becoming unresectable through dissemination, which is initially loco-regional, and systemic only in a later stage, dates from earlier times. In his 2011 Pulitzer prize-winning volume "*The Emperor of All Maladies*" [7], the oncologist Siddartha Mukherjee mentions the Scottish surgeon John Hunter (1728-1793), who in 1760 wrote: "*If a tumor is not only movable, but the part naturally so, they may be safely removed also. But it requires great caution to know if any of these consequent tumors are within proper reach, for we are apt to be deceived*". One of the reasons why Hunter's considerations are so valuable is because they are based on experience in the field – as it becomes abundantly clear to anyone visiting his vast collections, now contained at the head offices of the Royal College of Surgeons in Lincoln's Inn Fields (London). As the distinguished surgeon and pathologist Sir James Paget (1814-1899) (Stephen Paget's father) put it, John Hunter: "*collected everything, as if by natural disposition (…), and thus became – as no one else in his time – a comparative anatomist and pathologist*" [8]. Just over a century later, the American surgeon William Stewart Halsted (1852-1922) was the leading promoter of the conviction that malignant tumor growth occurs "in continuity". This concept of linear and centrifugal progression provides the basis for radical surgery – where, by 'radical', we mean the complete removal of the tumor and, in practice, aggressive surgery (Fig. 2). In Halsted view, "*breast cancer in spreading centrifugally preserves in the main continuity with the original growth*". It is also interesting to

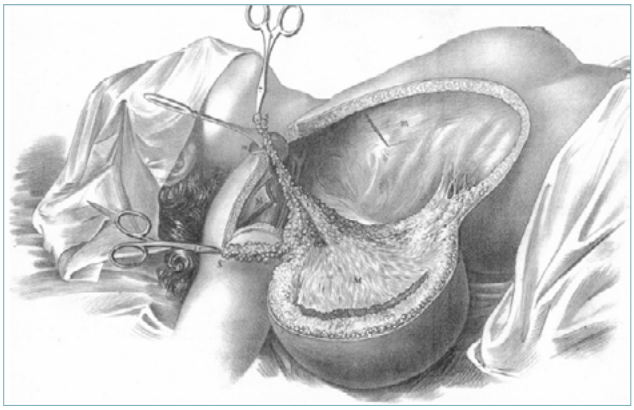

Figure 2. Halsted radical mastectomy.

read in the same paper how the liver metastatic processes were conceived by Halsted: "*The liver may be invaded by way of the deep fascia, the linea alba and the round ligament*" [9]. In his landmark paper [10] W.S. Halsted writes that "*the (deep) fascia serves for a time as a barrier, and is able to bring to a halt the spreading growth*" because "*I repeatedly found that the fascia was already carcinomatous, whereas the muscle was certainly not involved*". Therefore, "*the excision of the pectoral muscle or muscles means altogether a more complete operation, a more thorough removal of the fascia at the lower edges of the muscles and between the muscles*". A core part of this concept of radicalism is also the idea that lymph node metastases can serve as the pathway to further "in line" tumor growth in more distant nodes, and ultimately in visceral organs, as explained by Mark Wick in a recent historical review article [11]. Indeed, as stated by Halsted: "*I'm not sure that I have observed from breast cancer, metastasis which seemed definitely to have been conveyed by way of the blood-vessels*" [10]. Actually, the first modern investigations of bloodborne metastases in human and experimental animals were performed in the 1950s by Dale Rex Coman [12]. Today, it is almost too easy to criticize such a demiurgic-muscular view of surgery based on a simplified idea of the processes of invasion and metastasis, especially when we look at images of the crude, forequarter amputations found in the literature of the past. The outcome of Halsted's "radical mastectomy" were much better than the former approach, however, in terms of patient survival. Mukherjee [7] dedicates a whole chapter of his book to the dissolute life and extraordinary work of this great surgeon (Fig. 3), and comments on the fact that his patients unfortunately relapsed eventually, either locally or metastatically. It seems to have been left to Halsted's pupils to reveal the defect in his approach. If the tumor was localized from the start, then it would be adequately treated with a localized surgery and irradiation. Massively and manically removing lymph nodes and muscles would be pointless. Vice versa, if the breast cancer had already spread, then radical surgery seemed a pointless cruelty.

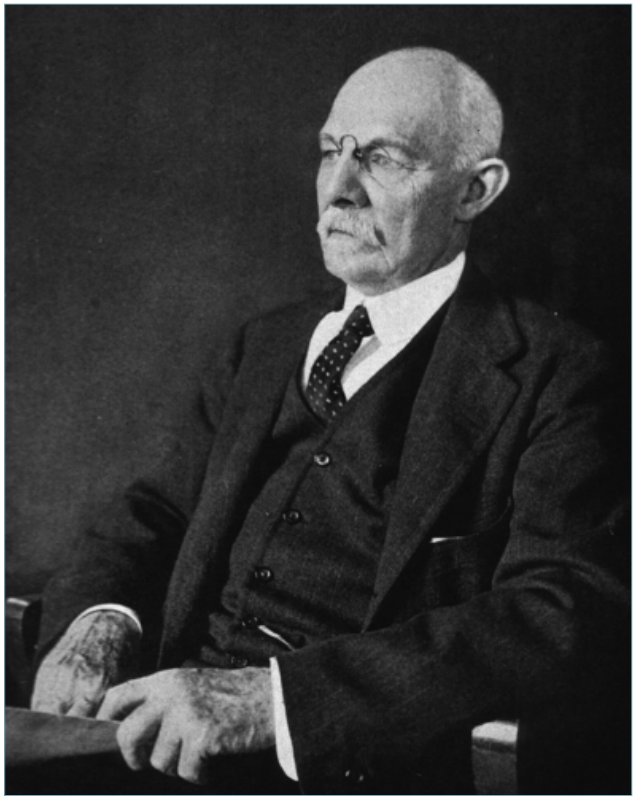

Figure 3. William Steward Halsted (1852-1922).

But just how widespread was still this idea of tumor progression as a linear process taking place in continuity and contiguity, and centrifugally, in the first half of the twentieth century?

We can get a good idea from a lengthy work published in *Pathologica* by A. Paladini in 1932 [13], entitled "*Pelvic infiltrations and lymph metastases in the evolution of prostate cancer*", *i.e.* of a tumor whose sistemic dissemination, like in breast cancer, can actually occur at a relatively early stage of the growth or the primary mass [14]. This study was an investigation on the anatomical conditions governing the diffusion of prostate cancer. The prostatic capsule, Denonvilliers' fascia, retropubic (Retzius) space, and paraprostatic pelvic connective tissue are described as dams against metastatic dissemination. The author, who was a urologist, failed to take into account the histology of the processes of extracapsular invasion of prostate adenocarcinoma, perineural infiltration, and seminal vesicle involvement. Here are a few significant excerpts of his article, expressing what was evidently a shared approach to interpreting the processes of invasion and metastasis.

"*If the fibromuscular tissue surrounding the retropubic space, because of its compact structure and continuity, is already able initially to contain the (neoplastic) processes occurring in the gland, so too can the prostatic capsule – given the aponeurotic nature of its layers – serve as a valid barrier that opposes any propagation, in certain directions at least*".

"*After spreading beyond the fibrous tissue around the space of Retzius, the neoplasm will expand more easily* (…) *Further expansion, beyond this regional stage of the blastoma (the tumor), is characterized by various pathways of communication (…) with the broad adjacent area of pelvic-subperitoneal connective tissue*".

"*In the final period, after going beyond the regional*

stage, the tumor invades all the tissues of the lesser pelvis, and this leads to disseminated prostatic-pelvic carcinosis".

Another interesting passage reads: "*A hard fibrous reaction consequently forms (…); because of this sclerotic tissue, which is merely an organic defense mechanism, course of the neoplasm is slowed and, for a long time, its rapid diffusion in continuity is prevented*". Together with the various anatomical layers, the peritumoral desmoplastic reaction is mistaken for a wall of defense against the neoplasm's dissemination, capable of containing and orienting it.

Finally, echoing Halsted's words on the stepwise fashion of lymph node dissemination, we find: "*As the tumor grows, the nearest lymph nodes are more or less rapidly invaded, and the first sites of metastases are precisely the hypogastric lymph nodes, followed by the external iliac lymph nodes, and sometimes also the aortic and inguinal lymph nodes*".

Self-evidently, the surgical response consistent with a similar interpretation of the processes could only be radicality at all costs [15]. However, despite the initial cancer control, enlarged (extrafascial, extraponeurotic) radical prostatectomy represented a challenging surgery, with a very high risk of massive blood loss, rectal injury, impotence and incontinence. Before the studies of Patrick Walsh [16] defining the correct surgical anatomy of the dorsal vein complex (Santorini's plexus), the location of the neurovascular bundle running the autonomic innervation of pelvic organs and the corpora cavernosa (cavernous nerves) as well as the anatomy of the sphincteric complex, virtually all men undergoing radical prostatectomy were impotent and quite all incontinent; hence, before 1980 only 7% of men with localized prostate cancer underwent surgery.

While the limited understanding of prostate cancer at the time is justified by the fact that it came largely from autopsy findings (it was only in 1930 that Ferguson described the use of needle aspirates for the microscopic examination of the prostate) [17], it has to be said that much the same view of the processes of invasion and metastasis of breast and prostate carcinoma was accepted for many other epithelial tumors as well, starting with lung cancer [11].

Conclusion

Unlike the world of literature and poetry, where even the best metaphor becomes weak if it is repeated, a good metaphor can be a useful working tool in the scientific sphere. The term "metastatic cascade", formulated in 1975 to describe a number of sequential events needed for the dissemination of cancer [18], is such a useful metaphor. Its use has generated working hypotheses and important results. It contains no trace of any role for the various extracellular matrices as a barrier to neoplastic infiltration. The steps in the interaction between neoplastic cells and the various micro-environments (the basal membrane, extracellular matrix, endothelium, blood, remote organs, etc.) have been clarified over time [19,20]. The complexity of the elements involved (biologic metastatic heterogeneity, different classes of adhesion molecules, proteolytic enzymes, cytokines, etc.) has increased over the decades, but the fundamental principles have not changed.

The founding idea is that tumor cells interact with the surrounding micro-environment, which is not simply a passive barrier. The dependence of the seed on the soil, or the interaction between seed and soil, is now widely accepted – whatever the seed (be it a cancer stem cell or a metastatic cell) and the soil (extracellular matrix, niche, endothelial cells). This idea of cross talk between neoplastic cells and microenvironment is possibly the most significant element handed down to us since Stephen Paget first formulated his seed and soil hypothesis more than 130 years ago.

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