

Cancer and the arts: metastasis – as perceived through the ages



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METASTASIS

Metastasis, originally from Greek, makes its entry in the English language probably in the late 16th century as a rhetorical term, implying ‘rapid transition from one point to another’.

In the extant literature from Greek antiquity to Byzantium (8th century BC to 1453 AD), over 360 entries for ‘metastasis’ and its derivatives are listed in the *Thesaurus Lingua Graeca*.¹ The word is first attested to the lyric poet Simonides (6th–5th century BC).

Ever since, *metastasis* has been used by philosophers, physicians, dramatists of comedy and tragedy, theologians, orators and others¹ but in a context unrelated to the meaning found in contemporary dictionaries—that is, *cancer dissemination*.

Metastasis in Greek means removal or migration, dislocation, but also departing from life.²

Plato³ and Aristotle⁴ used the term *metastasis* to discuss the change, by revolution or transition, of a political constitution.

In a medical context, *metastasis* means the *transference* of the seat of disease.²

In the texts of the Hippocratic corpus (c. 5th–4th century BC), there are at least nine entries for *metastasis* (μετάστασις), some in well-known treatises, such as the *Nature of Man* (De natura hominis); the *Sacred Disease* (De morbo sacro) and *Coan Prognostications* (Coacae Praenotiones), as well as *On Wounds* (de Ulceribus); in the second book *On Prognosis* (Praedictorum liber secundus); *On the nature of bones* (de Ossium natura) and in *Letters* (Epistolae). These entries, however, appear in a context, unrelated to cancer, a disease, nevertheless, amply, repeatedly and clearly described in the corpus.⁵

Galen (129 AD–c. 200 AD) in his commentary to Hippocrates’ Aphorisms, reiterates that *metastases of an ailment are named when its transference occurs from one part (of the body) to another*. Although this definition would fit the concept of metastatic cancer, it focuses on a statement by Hippocrates that epilepsy developing before puberty may resolve (in adulthood).⁶ In this context, metastasis

means also *lysis* or resolution of a disease such as epilepsy.

The Greek physicians of antiquity had a remarkable insight into the nosology of cancer,⁵ but it is uncertain whether they perceived metastases developing in organs distal to the primary site, as part of the neoplastic process, in the way it is understood in our time.

Aristotelis Kouzis, a Senior Lecturer at the University of Athens, conducted a systematic review of the oncological literature of ancient Hellenic medicine; his scholarly monograph, ‘*Cancer and the Ancient Greek Physicians*’ (in Greek) was published in Athens in 1902. In this treatise, which was awarded a prize by the Athenian Medical Society, kouzis does not include *metastasis* as a concept of cancer dissemination to distant organs.⁷

He argues, though, that the ancients were aware that infections could spread to different organs and that tumours could develop beyond the primary site. He was convinced that the Greeks were aware that cancer could involve regional lymph nodes; but for this process, the term used, Kouzis proposes, was *sympathy* (συμπάθεια), not metastasis.⁷

There is indeed ample evidence that invasion of adjacent tissues by cancer was recognised in antiquity.

Galen recruits his humoral theory to argue that black bile is responsible for the development of cancer and the more pungent it is, the more likely it is for the cancer to be ulcerated as it erodes the overlying skin.⁸ Leonidas, an Alexandrian surgeon (second century AD), in a thorough description of a mastectomy, writes: “and in the case of *carcinomata* which are **not** attached to the thorax, I use surgery in this manner...” He goes on to give a detailed account of the procedure, including the postoperative care.^{5,7}

As for involvement of regional lymph nodes, there is a reference by Hippocrates to inguinal lymphadenopathy developing in association with gynaecological cancer.⁵

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Six centuries later *sympathy* is invoked for the development of axillary lymphadenopathy from breast cancer. (Aëtius, quoting Leonidas and Archigenis), as cited by Kouzis.⁷

For the physicians of ancient Greece, *sympathy* (συμπάθεια) denotes primarily a physiological interaction between different organs. Soranus of Ephesus (c. 1st–2nd AD) talks about such *sympathy* between the uterus and the breasts: “there is a natural sympathy between the uterus and the breasts; so, as it (the uterus) enlarges during puberty so do the breasts enlarge correspondingly and whilst (in the uterus) the sperm is accomplished, the breasts prepare the milk in nourishment for those to be born; and on those pregnant women if we saw the breasts being shrivelled and coming together, we foretell a forthcoming abortion”.⁹

Dr DB Slack of Providence, in two consecutive papers submitted to the Editor of the *Boston Medical and Surgical Journal* (the precursor of the *NEJM*) on 28 August and 10 September 1843, discusses the meaning of these two concepts; the first paper is titled **Sympathy-Metastasis** and the second, in reverse order, **Metastasis-Sympathy**.^{10 11}

In the August paper, he writes “The literal meaning of sympathy, is the suffering or affection of two separate parts of the body at the same time. The term sympathy is derived from a Greek word signifying to suffer together”.

In the September paper, he argues that ‘metastasis, or the fancied change of diseases from one part of the system to another, is considered a result of the principle of sympathy. A remarkable instance of metastasis, he continues, is supposed to occur in that painful disease, the gout. This disease is supposed sometimes, to originate in the stomach, liver or intestinal canal, and to pass from these parts into the foot or the first joint of the great toe’.

Elsewhere he writes “Sympathy is again called into play to explain the connection supposed to subsist between the breasts and the uterus in the process of conception, gestation, and birth of the child”.

And he continues “The principle of sympathy does not work both ways. I have seen the most severe local affections of the breasts without the slightest particle of friendly participation on the part of uterus. In cancerous affections of the breasts, the uterus does not appear to be affected any more than the other parts of the body”. Here, again *sympathy* rather than *metastasis* is used to describe affliction of different organs of the body by cancer.

A search through the archives of the *NEJM* for the words metastasis AND cancer leads to the paper by Homer Gage, CANCER OF THE COLON, published in the *Boston Medical and Surgical Journal* on September 28, 1911. In this communication, appearing 9 years after Kouzis’ monograph, there is unequivocal use of the term metastasis to denote distant dissemination of cancer.¹²

Gage writes “It has been frequently observed that cancer of the sigmoid seems to retain its local character much longer than cancer in other parts of the large intestine, and that lymphatic involvement and visceral metastases occur much later. In 41 autopsies observed by Clogg, in less than 15% was there any metastasis, and that always in the liver”.

We encounter the word *diathesis* for predisposition, but *sympathy* is nowhere to be found in Gage’s, 1911 paper, in his discussion of cancer spreading.¹²

We may therefore assume that *metastasis*, as far as cancer is concerned, achieves its current meaning in the early 20th century.

Today, we remain intrigued by *metastasis*, a biological process considered highly inefficient, in that less than 0.01% of circulating tumour cells eventually succeed in forming secondary tumour growths.^{13 14}

And we are puzzled with the propensity of uveal melanoma to metastasise to the liver in 95% of cases, occasionally as many as 20 years or longer after enucleation of the eye harbouring the primary lesion, whereas this same tumour hardly ever metastasises to the brain.¹⁵ Clearly, these phenomena cannot be satisfactorily explained by anatomical–mechanical principles. Is this a haematogenous metastasis or is it an as yet unidentified *sympathy* between the choroid of the eye and the liver?

Perhaps, the emerging molecular imaging with ultrasound and similar technologies, will I day help to throw more light into this titillating relationship.^{16 17}

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