History and General Aspects of Tumor Grading

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Malignity only differs in degree.
Rudolph Virchow, 1860

1.1 History of Tumor Grading

The relationship between the tumor morphology and the clinical behavior of tumors has been known since the early studies of Rudolf Virchow (1821–1902) and the scientific beginnings of microscopic pathology. From the historical point of view, however, the first attempts to correlate the microscopic features of tumors with their biology and clinical behavior are traditionally attributed to David Paul von Hansemann (1858–1920) [1–3]. This German pathologist, who was a student of Virchow, studied systematically the microscopic pathology of tumors and in the 1890s published his pioneering observations on abnormal mitotic figures. He also introduced the terms *anaplasia* and *dedifferentiation* (German: *Entdifferenzirung*) and was the first to suggest that the clinical behavior of tumors could be predicted from their microscopic characteristics. His novel observations on microscopic tumor cell atypia, anaplasia, and asymmetrical mitoses were summarized in an 1897 book [3]. Von Hansemann's teaching and his book were at that time considered revolutionary and quite controversial, stimulating many scientific discussions [4]. Nevertheless, the book was apparently widely read, and it reappeared 5 years later in its second edition (Fig. 1.1). In contrast to many theoretical textbooks dominating the field of pathology, this treaty was based on meticulous microscopic study of tumors and could be considered "evidence based." It was illustrated with original drawings supporting the author's views of cancer (Fig. 1.2). The clarity of these illustrations is fascinating even today.

In the 1920s, Albert C. Broders of the Mayo Clinic pathology staff published his experience with grading of squamous cell carcinoma of the lip and skin and correlated the histologic grade with the outcome of the of the neoplastic disease in patients harboring these tumors (Fig. 1.3) [5, 6]. Broders implied that all malignant tumors could be divided into four groups, depending on the extent of tumor cell differentiation. He used a four-tiered system and classified tumors into those that contain 25, 50, 75 or 100 % incompletely differentiated of the cells. His ideas on grading of tumors were subsequently adopted by many others and applied to tumors in other organ systems.

Greenough was the first to propose the idea of histologic grading for breast cancers in 1925 [7]. He and his colleagues assigned a grade to tumors based on the overall evaluation of eight histologic features. Using a three-tiered grading system, these authors showed a clear association between tumor grade and the 5-year "cure" in their clinical-pathologic study. It is fair to say that all the current breast grading systems stem from his original ideas and the work from the early twentieth century.

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Die

mikroskopische Diagnose

der

bösartigen Geschwülste

von

Professor Dr. **David von Hansemann.**

Zweite Auflage.

Mit 106 Figuren im Text.

Berlin 1902.

Verlag von August Hirschwald.

N.W. Unter den Linden 68.

Fig. 1.1 Front page of the second edition of von Hansemann's textbook

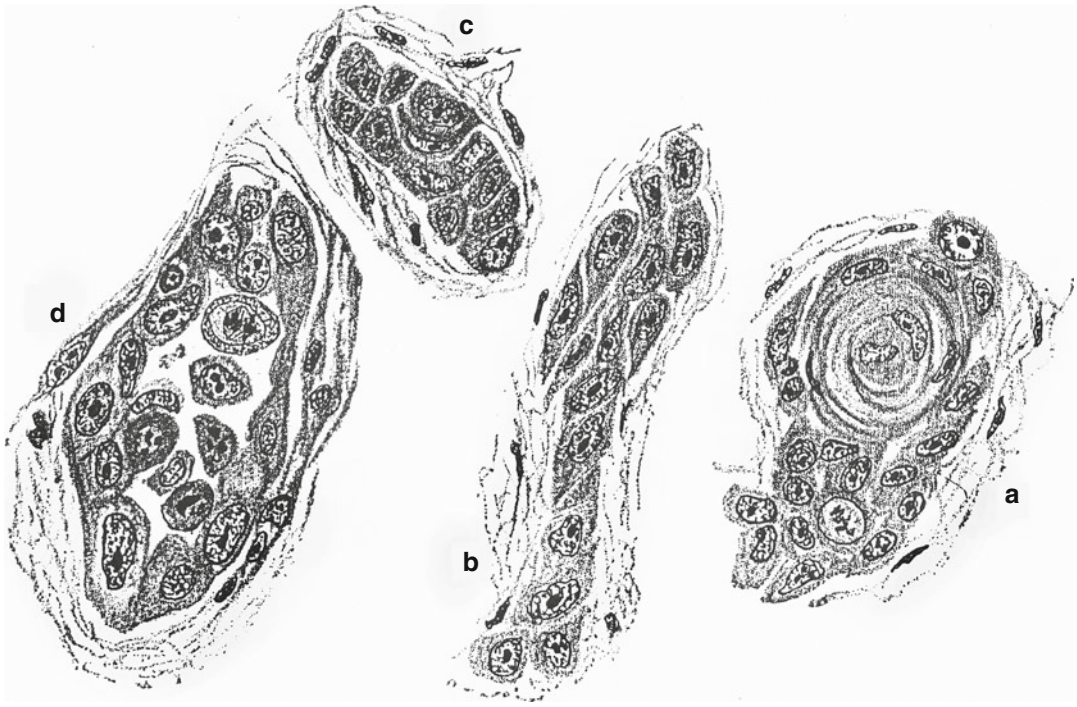

Fig. 1.2 Artist's drawing of squamous carcinoma cells (From Von Hansemann D (1902) Die mikroskopische Diagnose der bösartigen Geschwülste, 2nd edn. A. Hirschwald, Berlin)

The concepts and conclusions drawn from these early studies have been used and modified repeatedly during the following years [8–10]. Some of the early students of grading combined it with staging, and their eponymous systems, such as the Dukes system for classifying colonic cancer [8], survived up to modern times. For breast cancer alone, more than 10 grading methods and their modifications have been proposed. By the late 1990s, over 40 histologic grading systems for prostatic carcinoma were proposed [11].

Despite a plethora of longitudinal retrospective and prospective studies showing the usefulness of microscopic grading, the idea of routine tumor grading did not gain much popularity among clinicians and pathologists up to 1970s. This was partly due to the complexity and subjectivity of some grading systems and partly due to the limitation of treatment options corresponding to different grades of the tumor. However, as the treatment options multiplied, the need for better stratification of patients became imperative. Carriaga and Henson [12] found that the overall frequency of grading increased over the 15-year period of 1973–1987 by 18 % for all sites combined: 65 % of all cancers were graded in 1983–1987, compared with 47 % in 1973–1977.

Today there is an overwhelming consensus that tumor grading has in many instances not only a prognostic value, but also it might have a significant impact for choosing optimal treatment for particular tumors (predictive value).

1.2 General Principles of Tumor Grading

The main principle of tumor grading, originating from Broders' earlier work, is to identify parts of the tumor that are differentiated and express the extent of differentiation as a percentage of the entire tumor. The grading method is to use standard light microscopic interpretation of hematoxylin and eosin (H&E)-stained tissue sections. Some earlier grading

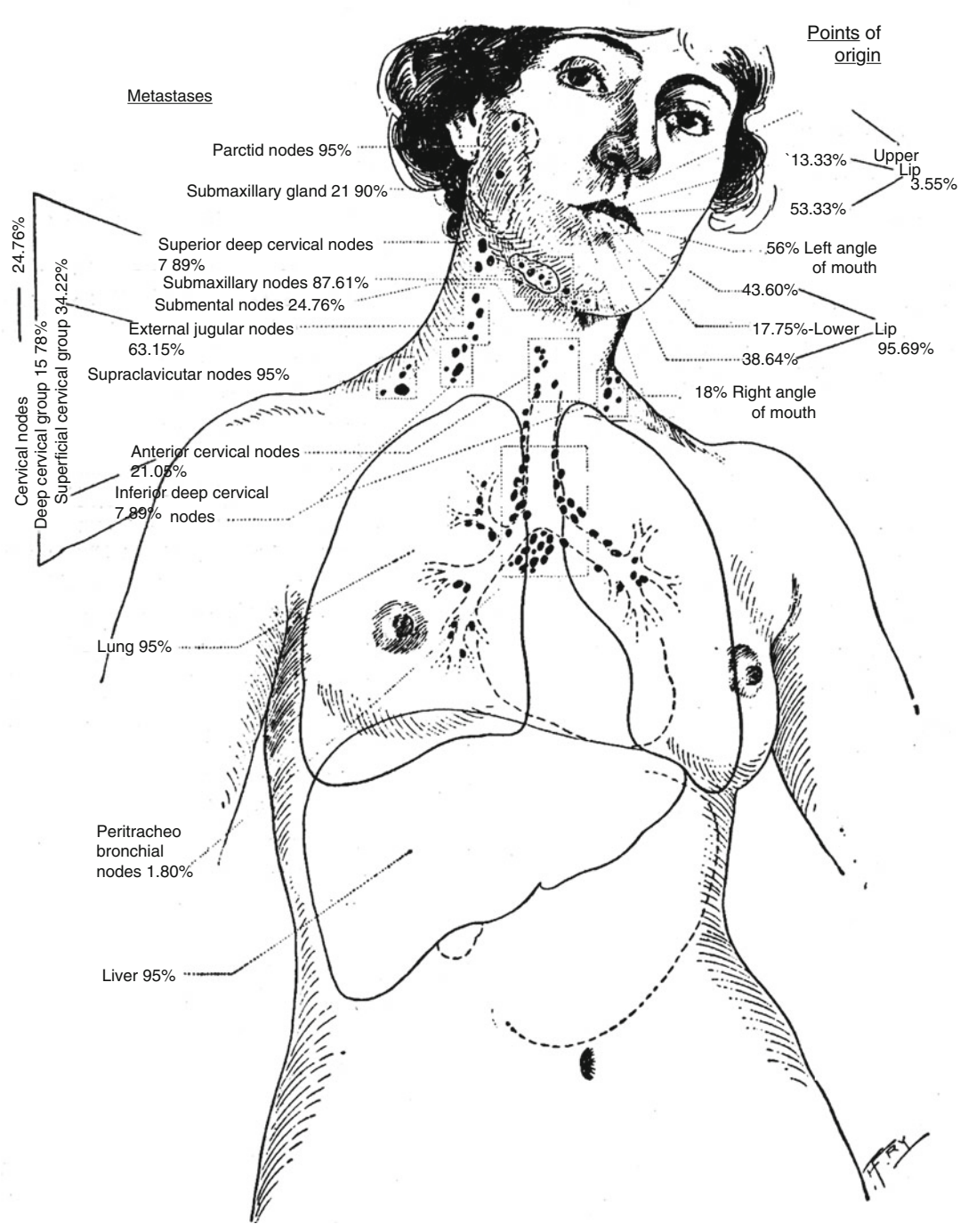

Fig. 1.3 Broders' seminal paper on grading of tumors (Broders [5])

systems required grading of up to 15 histologic features which included grading of growth pattern, cell morphology, and tumor stromal response [13]. Such elaborate systems were found to be, however, cumbersome, unreliable, and not always reproducible. Therefore, a good grading scheme should be simple, easy to perform, reliable, and reproducible and should be

able to pass the test of time and prove to be clinically useful [14].

The grading process in general includes assessment of both the architectural and cytologic features of a tumor. Some grading systems focus, however, mainly on one histologic feature. For example, grading of prostatic adenocarcinoma is based entirely on the architecture feature, and grading of renal cell carcinomas is based entirely on their nuclear features. In general, the most poorly differentiated part of the tumor determines the final tumor grade, with the exception of the Gleason grading system for prostatic adenocarcinoma in which the two most prevalent patterns are used for grading. It is worth mentioning, however, that even such well-established systems as the Gleason grading of prostate carcinoma are still being modified; a need for the identifying a tertiary pattern has been formulated, and the reporting of cancer grades was found to vary even among the urologic pathologists [15, 16].

So far, all grading systems are designed for grading the primary untreated tumor. Attempts have been made to apply the same grading scheme for metastatic foci and residual tumors after radiation and/or chemotherapy. Currently, there is no general consensus on this issue.

1.3 Ancillary Methods Used in Tumor Grading

Almost all systems for grading of malignant tumors are currently based on morphologic evaluation of tumor sections under the microscope. Several improvements of the time-honored microscopic approach have been recommended, but few of these have been adopted in routine surgical pathology practice. Probably the most notable exception is the immunohistochemical staining with the antibody MIB-1 (Ki-67), recognizing cell proliferation. This immunohistochemical technique has been proposed as an objective supplement of several tumor-grading systems, including the grading of breast carcinoma, brain astrocytoma, and lymphoma [17, 18]. It is expected that with advanced understanding of diseases and development of new technology, prognostic biomarkers and genetic information may be incorporated in tumor grading in the future.

The prognostic and predictive value of microscopic tumor grading can be enhanced by using other immunohistochemical methods [17–21]. For example, in breast carcinoma, immunohistochemical data with antibodies to estrogen receptor, bcl-2 gene product, and Her2/neu have predictive value in both univariate and multivariate analysis and are useful for predicting the patients' response to specific therapy [18]. In most instances however, there is no consensus on the value of these ancillary methods. For example, the International Consensus Panel on cytology and bladder tumor markers could not agree on the value of multiple markers in predicting tumor recurrence, progression, metastasis, or response to therapy [19]. This Panel evaluated various prognostic indicators and classified them into six groups:

- Microsatellite-associated markers
- Proto-oncogenes/oncogenes
- Tumor suppressor genes
- Cell cycle regulators
- Angiogenesis-related factors
- Extracellular matrix adhesion molecules

The members of the Panel concluded that certain markers, such as Ki-67 and p53, appear to be promising in predicting recurrence and progression of bladder cancer, but the data are still incomplete. It was also concluded that no consensus should be attempted until major prospective studies are performed and definitive criteria for test positivity are defined. Further recommendation included performing studies of clearly defined patient populations, standardization of techniques for evaluating the markers, and clearly specified clinical endpoints with good statistical documentation.

The use of ancillary methods has been especially championed by the neuropathologists who have used several techniques to estimate the proliferative potential of brain tumors. As summarized in a recent review article by Quinones-Hinojosa [21] in addition to immunohistochemical staining with antibody Ki-67 (MIB-1), such measurements can include bromodeoxyuridine labeling

index (BrdU LI), flow cytometry (FCM), and staining for the proliferating cell nuclear antigen (PCNA) and argyrophilic nucleolar organizing regions (AgNOR). At the present time, MIB-1 and AgNOR are the simplest and most reliable of these techniques. Radiographic studies such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and most recently magnetic resonance spectroscopy (MRS) used as follow-up measures have the potential to provide an assessment of tumor proliferation without the need for invasive measures.

1.4 Clinical Value of Tumor Grading

Data obtained by tumor grading are usually combined with those obtained by tumor staging and other clinical approaches and are then evaluated by multivariate analysis. In most studies of this kind, it has been shown that tumor grade contributes to the multivariate prognosis, but in some, it was shown that the grading could be in itself a valid prognosticator even in a univariate analysis. Henson [9] in 1988 published a study on the relation between tumor grade and patient outcome. More than 500,000 cases from 15 anatomic sites with up to 9-year follow-up were reviewed. The results showed that stage by stage, the grade further subdivided the overall survival rates for each site into distinct subsets that were significantly different. Carriaga and Henson [12] later performed a similar study and demonstrated that the histologic grade is a strong predictor of outcome that refines the prognostic information provided by the stage of disease. There are numerous other studies reported in the literature showing that microscopic tumor grading has independent prognostic value [14–17].

Due to the availability of different treatment options, tumor grading now has an additional clinical value as guidance for therapy choice. While surgical resection may suffice for a low-grade tumor, additional radiation and/or chemotherapy may be necessary for high-grade tumors. By combining grading with staging and clinical data, one may construct nomograms which may predict the outcome of the treatment, disease-free survival, or cure rate. This may be true for many epithelial tumors, brain tumors, as well as sarcomas of bones and soft tissues, even though many tumors still do not lend themselves to grading [22, 23]. Nevertheless, most tumors can be stratified microscopically, and if the grade assigned to them is combined with grading and other clinical data, it may serve as a powerful predictor of clinical outcome of neoplastic disease, as well as for choosing the appropriate therapy for many cancer patients.

1.5 Perspective

Grading of tumors has been an integral part of the pathologic examination of biopsies and surgically resected tumors for close to 100 years. During that period, numerous studies have been performed on the value of grading, and numerous modifications of various systems have been proposed and tested. Grading of tumors could be thus considered as a work in progress, and additional efforts to improve the existing schemes are obviously necessary. This will require additional prospective studies, improvement of the intra- and interobserver variability, statistical evaluation of reproducibility, and correlation with the end-point treatment outcome results.

Current systems for grading tumors are far from perfect and ideal. New modifications of old systems are constantly tested, and many improvements are reported, often validated in practice or reviewed in view of the contributions of the new technologies [23, 24]. Controversies persist, but still, the general consensus of pathologists, surgeons, and clinical oncologists is that the tumor grades deserve to be part of routine pathology reports for most tumors and should be performed by diagnostic pathologists as meticulously as the situation requires [25]. In concordance with this approach, the Association of Directors of Anatomic and Surgical Pathology (ADASP) also recommended that tumor grades be included in standardized surgical pathology reports, implying that such reporting could contribute positively to patient care [26]. Although there

are still no universal position papers on the use of modern technologies, intuitively, most of us also believe that the technologic advances in the field of molecular and cancer cell biology will significantly contribute to the grading of tumors and make it even more clinically relevant than ever before.

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