History of Medicine

From Trephining to Genotyping: A brief look at the history of Neuro-oncology

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The field of neuro-oncology has shown dramatic advancements over the past several years after a period of relative quiet throughout much of the late 20th century. We are at a pivotal turning point in the field as genotyping and further advances in the use of chemotherapy continue to push the borders of brain tumor therapy. Thus, it seems fitting at this point in history to have a brief look at the origins of neuro-oncology and the more recent developments that are advancing the field at a rapid pace. This article takes its readers through a tour of the origins of neurosurgery and then analyzes the more recent multimodal approach to neuro-oncology to give some perspective and appreciation of this rapidly evolving field.

This article has been reviewed by Dr. Chris Watling.

Introduction

Despite having developed tremendously over the past several centuries, the field of neurology is one area in medicine that is continuing to show rapid growth in all facets even today. With improvements in imaging and genetic analysis, neurology is growing by leaps and bounds, transforming a specialty that was primarily diagnostic a few decades ago to one in which interventional procedures and curative treatments are becoming increasingly common.1-3

Another field which has continued to improve, thanks in large part to the advent of radiotherapy over the past century and rapid developments in the field of chemotherapy, is that of oncology. Cancer research has plastered the pages of the lay press on a daily basis over the past decade and continues to make headlines within the scientific community as one of the fastest evolving fields in medicine today.

The field of neuro-oncology, in contrast, had a period of quiet in the last two decades of the 20th century as research and trials were unable to keep up with developments in other areas of medicine. The last decade, however, has seen progress in this blossoming field with the publication of several landmark trials. This article will place recent developments in a historical perspective, beginning with early neurosurgical work and concluding with a look at where current cutting-edge research is leading us today.

The beginnings and development of neurosurgery

Pre-1850: From trephining to anesthetics

Some form of neurosurgery existed in ancient societies, as evidence of trephining can be traced back over three thousand years to Ancient Egypt.4 However it was in 1573 that Giovanni Croce published Chirurgiae, a book which has the first depictions of a neurosurgical operation taking place.5 It was not until 1846 when William Morton discovered the usefulness of sulphuric ether, the first modern anesthetic, on the 16th of October at Massachusetts General Hospital6, that the field of neurosurgery began to flourish.

1850-1900: Removing tumours

These developments caused a flurry of activity on the surgical front and it was in 1879 that Scottish surgeon William MacEwen described what is believed to be the first removal of a dural based tumour.7 It was a few years later in 1884 when British physician Alexander Bennett diagnosed a cerebral tumour in a patient of his and decided that surgical intervention would be the best approach. He asked surgeon Richman Godlee to operate and it was Godlee who carefully removed the tumour from deep within the cortex. The patient died soon after of infection but autopsy results indicated that this was perhaps one of the first gliomas to have been successfully excised from a patient.8
1900-1950: Cushing to the gamma-knife

Surgical developments continued gradually over the next several decades and it was in the early 1930s when Harvey Cushing, a Professor of Surgery at Harvard Medical School, reported a remarkable decrease in the mortality of neurosurgical patients over the previous decade. After statistically analyzing over two-thousand verified tumours, Cushing showed significant decreases in the mortality rates of neurosurgery used to treat acoustic neuromas (25.0 to 4.4%), gliomas (30.9 to 11.1%), meningiomas (21.0 to 7.7%), and many other cerebral tumour subtypes. These advancements are simply one example of Cushing’s many significant contributions to the field of neurosurgery in the first half of the 20th century.

The next major development in the field of neurosurgery was the development of stereotaxic surgery by Ernest Spiegel in 1947 as he used a stereotaxic frame to accurately localize sites for the biopsy and treatment of neurological lesions. In 1950, Lars Leskell developed Spiegel’s apparatus to create the concept of stereotaxic radiosurgery using the ‘gamma knife’. Leskell thus became the first physician to be able to deliver radiation in a focused manner to localizable tumours within the brain.

Post-1950: Microsurgery and beyond

Neurosurgical developments continued over the next several years and it was in the late 1960s that Gazi Yagarsil, proclaimed “Man of the Century 1950-1999” by the well-respected scientific journal Neurosurgery, developed the concept of microsurgery. He developed the idea of performing surgery on small and delicate tissues with the aid of an operating microscope. This advancement in the field was unparalleled in its significance over the second half of the 20th century as it allowed surgeons to operate much more efficiently on the very fine and delicate structures within the brain.

Thus, in just over a century since the advent of modern anesthetics and the beginnings of surgery as we know it today, the field of neurosurgery developed significantly, allowing a safer and more precise approach to brain tumour resection. Advances in the field have continued over the past several decades but this serves as an introduction to the origins of the field of neuro-oncology as it is known today.

Beyond neurosurgery

The first step: Combining surgery and radiation therapy

In 1978 a landmark study by the Brain Tumor Study Group and the National Cancer Institute (NCI) reported on a prospective, randomized-controlled study which analyzed the use of a chemotherapeutic agent, 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU), and/or radiation therapy in surgical patients who were found to have anaplastic glioma. The results of this pivotal trial provided clear evidence for the benefit of radiotherapy as it prolonged survival from 14 to 36 weeks versus controls. The addition of BCNU alone produced a statistically insignificant increase in survival and the use of adjuvant BCNU to radiotherapy also yielded unimpressive results. This study paved the road for treatment over the next quarter century as postoperative cranial radiation became standard treatment for patients with malignant gliomas, but the use of chemotherapy remained on the sidelines for the time-being.

A side-step: Genotyping and brain tumours

It would be at the University of Western Ontario in London, Canada that the next major development in neuro-oncology would occur, over 20 years after the last milestone. In research that began a decade earlier, it was reported in 1998 that anaplastic oligodendrogliomas with coincident loss of chromosome 1p and 19q had increased susceptibility to chemotherapeutic intervention. The results were monumental and led to a flurry of activity within the neuro-oncological field in attempts to more carefully delineate genetic factors predictive of treatment response or prognosis. The use of genotyping and other forms of cutting-edge medical technology are thus serving an important role in the development and progression of neuro-oncology.

The second step: Surgery and chemotherapy... the relationship begins

Almost 25 years after the landmark Brain Tumor Study Group and NCI trial implicated that BCNU had a minimal role in the treatment for malignant glioma, the results a multinational randomized placebo-controlled trial that used BCNU wafers (Gliadel wafers) to complement surgery were published in April of 2003. The results indicated that the insertion of a small biodegradable polymer containing BCNU into the resection cavity at the time of surgery for malignant glioma increased median survival from 11.4 to 13.1 months versus the placebo group. Although the results may seem insignificant to most, this was the single largest increase in survival of malignant gliomas post-surgery in over 25 years.
The third step: Surgery, chemotherapy, and radiation therapy – finally united

In March 2005, Stupp and colleagues published the results in a multicentre international randomized-controlled trial addressing treatment of glioblastoma multiforme. In this study, patients were randomized, following maximum possible surgical resection, to receive either radiation with concurrent chemotherapy with Temozolomide followed by six cycles of adjuvant Temozolomide or radiation alone. Median survival in the radiation plus Temozolomide group was 14.6 months compared with 12.1 months in those receiving radiation alone. However the research made waves among the neuro-oncological community as it also indicated that combined treatment with radiation plus temozolomide led to two-year survival rates of 26.5% versus only 10.4% in those given radiation alone. This near tripling of 2-year survival rates was absolutely unheard of in the field of neuro-oncology.

Along with the publication of the landmark temozolomide trial came evidence by Monika Hegi that silencing of the DNA-repair gene O6-methylguanine-DNA methyltransferase (MGMT) is positively correlated to a significant survival advantage in those with glioblastoma multiforme. This finding illustrates the pivotal role that molecular analysis is playing in the advancement of brain tumour.

Future Directions: A rapidly evolving field

After nearly twenty years of largely unsuccessful efforts, the field of neuro-oncology has shown considerable developments over the past decade. With continued advancements in the fields of radiology, gene therapy, and cancer therapeutics in general, neuro-oncology has tremendous potential for development over the coming years. We are thus clearly at a frontier in the treatment and management of brain tumours and this brief look at past achievements in neuro-oncology provides perspective on future advancements.

References