

## A Voice From the Past: Rediscovering the Virchow Node With Prostate-specific Membrane Antigen-targeted $^{18}\text{F}$ -DCFPyL Positron Emission Tomography Imaging



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More than 150 years ago, German pathologist Rudolf Ludwig Karl Virchow (1821-1901) described the finding of the involvement of the left supraclavicular node in gastric cancer.<sup>1</sup> It is now known that a number of abdominal and thoracic malignancies have a propensity to metastasize to this anatomic site, which is commonly referred to as Virchow node. Cancers known to spread to Virchow node include malignancies of the lung, pancreas, and esophagus, and adenocarcinoma of the gastric corpus, kidney, ovary, testicle, stomach, corpus uteri, cervix uteri, colon, and rectum.<sup>2</sup> Metastasis to Virchow node has also been reported in men with prostate cancer; however, this has generally been observed at a low frequency of only 0.5%.<sup>3</sup>

In recent years, positron emission tomography (PET) radiotracers targeting prostate-specific membrane antigen (PSMA), including  $^{68}\text{Ga}$ -PSMA-11 and  $^{18}\text{F}$ -DCFPyL, have been increasingly used to image men with prostate cancer.<sup>4,5</sup> PET imaging with these agents offers greatly improved sensitivity over conventional imaging modalities for detecting low volume sites of tumor burden.<sup>6,7</sup> Because of the outstanding sensitivity afforded by PSMA-targeted PET, it can be directly visualized that many patients with advanced prostate cancer can harbor disease within Virchow node (Fig. 1).<sup>3,7-10</sup> This observation has served as an opportunity to re-explore the exemplary life and career of Rudolf Ludwig Karl Virchow.

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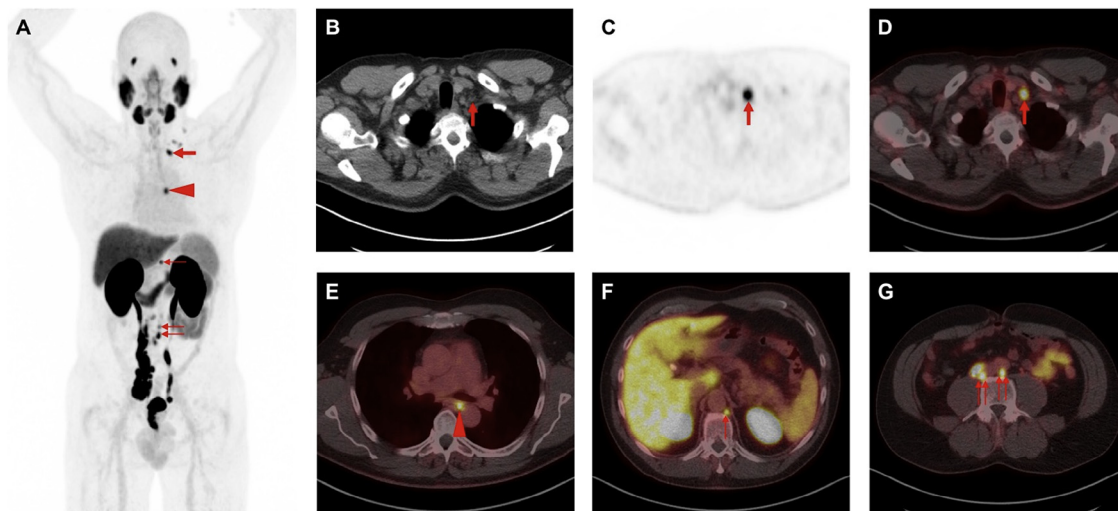
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### RUDOLF LUDWIG KARL VIRCHOW—“POPE OF MEDICINE” IN THE 19TH CENTURY AND SOCIAL REFORMER

Remembered as the most influential pathologist in the 19th century, Virchow was also famous as a liberal politician and as one of the leaders of the “Deutsche Fortschrittspartei” (German Progressive Party), the liberal political movement in Germany. In a time of competing political ideologies including nationalism, socialism and conservatism, the “Progressive Party” led the opposition to the constitutional forces of the Prime Minister of Prussia, Otto von Bismarck. However, because of his role in the 1848 “Märzrevolution” (March Revolution), Virchow was finally forced to leave Berlin and was subsequently appointed as the first Chair of Pathological Anatomy at the University of Würzburg in 1849.<sup>11,12</sup> Five years later, the Charité Berlin reassigned him as the first Chair of Pathological Anatomy and Physiology due to his increasing international popularity and reputation.<sup>11,13,14</sup> Known as the father of cellular pathology, Virchow established the journal “*Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*” in a close collaboration with his friend



**Figure 1.** Images from a  $^{18}\text{F}$ -DCFPyL PET-CT scan in a 57-year-old man with untreated, biopsy-proven Gleason 5 + 4 = 9 prostate cancer with serum prostate specific antigen level of 109.2 ng/mL. **(A)** Whole-body maximum intensity projection image demonstrates extensive adenopathy including a left supraclavicular Virchow node (red arrow) as well as radiotracer-avid lymph nodes in left cervical levels IV and V, the mediastinum (red arrowhead), the retrocrural space (thin red arrow), the retroperitoneum (double thin red arrow), and the pelvis. The **(B)** CT, **(C)** PET, and **(D)** PET-CT axial images at the level of the Virchow node show that its small size (5-mm short axis, red arrows) would make it occult on conventional anatomic imaging and indicate the importance of molecular imaging with a PSMA-targeted agent to uncover this site of disease. Additional axial PET-CT images through **(E)** the mediastinum, **(F)** the retrocrural space, and **(G)** the retroperitoneum demonstrate additional involved lymph nodes (red arrowhead in **[E]**, thin red arrow in **[F]**, and double thin red arrow in **[G]**) and suggest a pathway for involvement of the Virchow node, that is, the cancer likely spread up to the cisterna chyli in the proximity of the retrocrural node, then through the thoracic duct where it was able to establish sites of metastasis in both the mediastinum and left supraclavicular fossa. CT, computed tomography; PET, positron emission tomography; PET-CT, positron emission tomography-computed tomography; PSMA, prostate-specific membrane antigen. (Color version available online.)

Benno Reinhardt (1819-1852). Pursuing the goal of transforming the esoteric medicine in Germany to a scientific discipline, this journal is still with us today and is now known as “Virchows Archiv”, the official journal of the European Society of Pathology.<sup>15</sup>

As a broadly influential thinker of his day, Virchow’s career in social science remains equally as remarkable as his work in medicine. More specifically, he is credited with founding the newspaper “*Die medicinische Reform*” (Medical Reform), popularizing the term “social medicine,” and promoting the concept of physicians serving as “attorney(s) of the poor.” One of his most famous contributions in medical literature is the “*Report on Typhus Epidemic in Upper Silesia*.” Asked by the Education Minister of Prussia, Virchow investigated the 1848 typhus epidemic in Upper Silesia (now within the borders of Poland) and stated that Prussian authorities had failed in preventing the outbreak of this devastating disease. Outlining a revolutionary program, Virchow emphasized the urgent need for improvement of social conditions in this area, which are democratic self-government, disestablishment of the Catholic Church, and agricultural cooperatives.<sup>16-18</sup> Another example of his contribution to social medicine is his report “*Reinigung und Entwässerung Berlins*” in which, through a combination of

political power and scientific knowledge, he pushed the construction of the first sewer system of Berlin.<sup>19</sup>

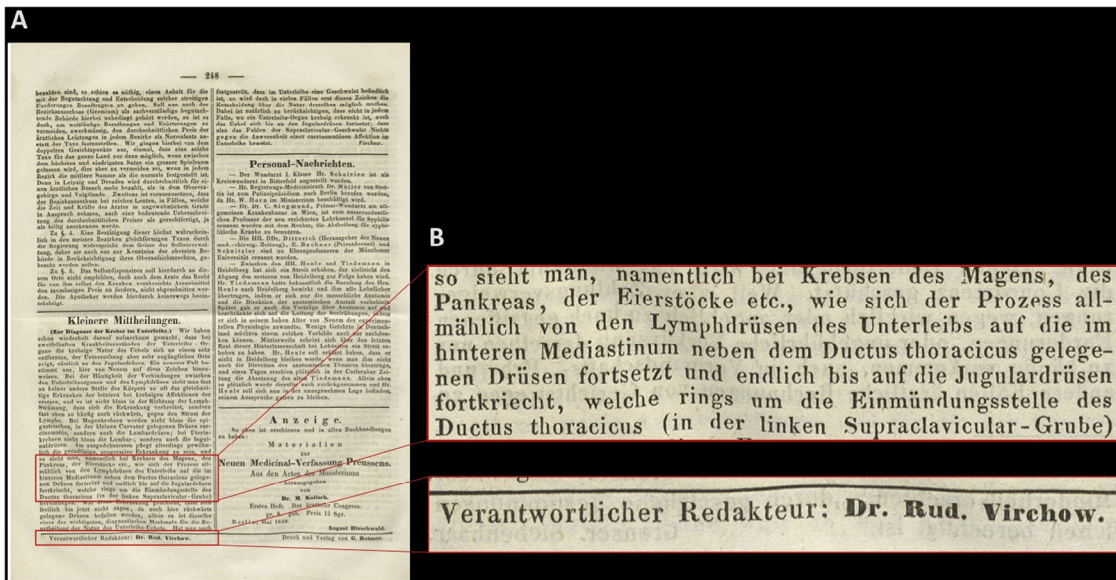
## VIRCHOW AND HIS AFTERMATH

With close to 2000 publications, Virchow has made major contributions to the field of cellular pathology and should be remembered for the introduction of certain medical terms that are still used today; Virchow defined the term “embolus” along with its thrombosis mechanism, the word “amyloid” and its reaction with iodine and sulphuric acid in the brain, and the term “granuloma.”<sup>11,20,21</sup>

## THE VIRCHOW NODE

Indisputably, the first description of an enlarged supraclavicular lymph node involved in metastatic malignancies dates back to Virchow. In 1848, he outlined in his article “*Zur Diagnose der Krebse im Unterleibe*” (Fig. 2):

*...namentlich bei Krebsen des Magens, des Pankreas, der Eierstöcke, etc., wie sich der Prozess allmählich von den Lymphdrüsen des Unterleibs auf die im hinteren Mediastinum neben dem Ductus thoracicus gelegenen Drüsen fortsetzt und*



**Figure 2. (A)** Original German article, “Zur Diagnose der Krebse im Unterleibe” by Rudolf Karl Ludwig Virchow, published in the *Medicinische Reform* (45:248) in 1848. The article is within the section titled “Kleinere Mittheilungen” (Brief Communication). Description of the Virchow node and the name of the author (Virchow) were both highlighted in a red frame. **(B)** Excerpt of “Zur Diagnose der Krebse im Unterleibe” showing the magnified paragraph of the Virchow node description (upper red frame). The lower red frame highlights the name “Dr. Rud. Virchow”, who is the author of the article and the editor-in-chief of the journal “*Medicinische Reform*”. (Universitätsbibliothek Heidelberg/Zur Diagnose der Krebse im Unterleibe/Die *Medicinische Reform* + Extrabl. [Signatur: Friedreich 297: 1-52.1848-49]; Seite 248). (Color version available online.)

endlich bis auf die Jugulardrüsen fortkriecht, welche rings um die Einmündungsstelle des Ductus thoracicus (in der linken Supraclavicular-Grube...<sup>1</sup>

This part has been translated by Morgenstern in 1979:  
 ...Thus, particularly in cancer of the stomach, the pancreas, the ovaries, etc. the process gradually spreads from the glands of the lower abdomen to the glands in the posterior mediastinum along the ductus thoracicus and finally involves the jugular glands around the junction of the ductus thoracicus (in the left supraclavicular fossa)....<sup>22</sup>

In 1889, Charles-Emile Troisier (1844-1919) also reported on the findings in 27 cases of gastric carcinoma and noted a palpable, hard, left supraclavicular node being present.<sup>23</sup> It has been thought that the cancerous enlargement of the left supraclavicular node at the junction of the thoracic duct and the left subclavian vein, and the tendency of gastric carcinoma to metastasize toward this region are related to tumor emboli migration through the thoracic duct. The thoracic duct is a continuation of the cisterna chyli at the L1 level, which then enters the thoracic cavity through the aortic hiatus and continues in the posterior mediastinum between the aorta and azygos vein.<sup>24</sup> The duct drains lymphatic fluid into the angle of the left subclavian and internal jugular veins. The end node of the thoracic duct is the so-called Virchow node and is located near or at this jugulo-subclavian venous junction.<sup>25</sup> The involvement of the Virchow node by metastasis can be seen in several types of cancer. Viacava and Pack investigated 4365 patients suffering from abdominal and thoracic tumors

and found an enlarged Virchow node in 2.8% of the patients.<sup>2</sup> The highest frequency was observed in patients suffering from cancers of the lung, pancreas, esophagus, kidney, ovary, testicle, stomach, prostate, corpus uteri, cervix uteri, and rectum.<sup>2</sup> Despite its first description more than 150 years ago, the underlying anatomy of the thoracic duct end node has just been investigated more recently. More specifically, in 2005, Mizutani et al found that the thoracic duct is divided into 3-10 several collateral ducts and these ducts surround the Virchow node.<sup>25</sup>

## CONCLUSION

The first description of the pathologic enlargement of the left supraclavicular node in gastric cancer was provided by Virchow in 1848. A number of other malignancies are now known to spread to this anatomic site. Whereas prostate cancer has not classically been thought to have a propensity for metastasizing to the Virchow node, advances in molecular imaging have revealed the contrary. The prevalent involvement of the Virchow node in prostate cancer has likely been underestimated in the past due to our inability to effectively characterize non-pathologically enlarged lymph nodes in this patient population. More than one and a half centuries after its first description, this in vivo detection of supraclavicular lymphadenopathy using prostate molecular imaging emphasizes the importance of the insightful and visionary work of Dr. Virchow. Further studies on the nature of the prostate cancer cells that are disseminated to the Virchow node may shed light on the

mechanism of prostate cancer metastases, the transition from the oligometastatic to the polymetastatic state, and the tumor microenvironment needed to maintain prostate cancer cells within this unique lymph node. However, if one might consider a molecular imaging approach to obtain specimen from the Virchow node (eg, by performing PET-guided biopsies), the costs for those types of studies have to be taken into account and the risk should be balanced against the clinical need.

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