

Review

## Thymic carcinomas and thymic neuroendocrine tumors: a tribute to Dr. Juan Rosai

Luca Di Tommaso<sup>1,2</sup>, Edoardo Pescarmona<sup>3</sup>, Arianna Di Napoli<sup>4</sup>, Libero Lauriola<sup>5</sup>, Mirella Marino<sup>3</sup>, Alexander Marx<sup>6</sup>, Philipp Ströbel<sup>7</sup>

<sup>1</sup> Department of Biomedical Sciences, Humanitas University, Milan, Italy; <sup>2</sup> IRCCS Humanitas Research Hospital, Milan, Italy; <sup>3</sup> Department of Pathology, Regina Elena National Cancer Institute, Rome, Italy; <sup>4</sup> Department of Clinical and Molecular Medicine, Sapienza University, Sant'Andrea Hospital, Rome, Italy; <sup>5</sup> Department of Pathology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma-Università Cattolica del Sacro Cuore, Rome, Italy; <sup>6</sup> Institute of Pathology, University Medical Center Mannheim, University of Heidelberg, Germany; <sup>7</sup> Institute of Pathology, University Medical Center Göttingen, University of Göttingen, Germany

### Summary

Throughout his career, Dr. Juan Rosai greatly impacted our understanding of mediastinal tumors, both as a scientist and as a teacher. This review highlights his manifold contributions in the field of thymic carcinomas and thymic neuroendocrine tumors from a historical perspective.

**Key words:** thymic carcinomas, thymic neuroendocrine tumor, Juan Rosai

Received and accepted: October 19, 2021

### Correspondence

Luca Di Tommaso  
Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy; IRCCS Humanitas Research Hospital, via Manzoni 56, 20089 Rozzano, Milan, Italy  
E-mail: luca.di\_tommaso@humanitas.it

### Conflict of interest

The Authors declare no conflict of interest.

**How to cite this article:** Di Tommaso L, Pescarmona E, Di Napoli A, et al. Thymic carcinomas and thymic neuroendocrine tumors: a tribute to Dr. Juan Rosai. *Pathologica* 2021;113:371-376. <https://doi.org/10.32074/1591-951X-536>

© Copyright by Società Italiana di Anatomia Patologica e Citopatologia Diagnostica, Divisione Italiana della International Academy of Pathology



OPEN ACCESS

This is an open access journal distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license: the work can be used by mentioning the author and the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

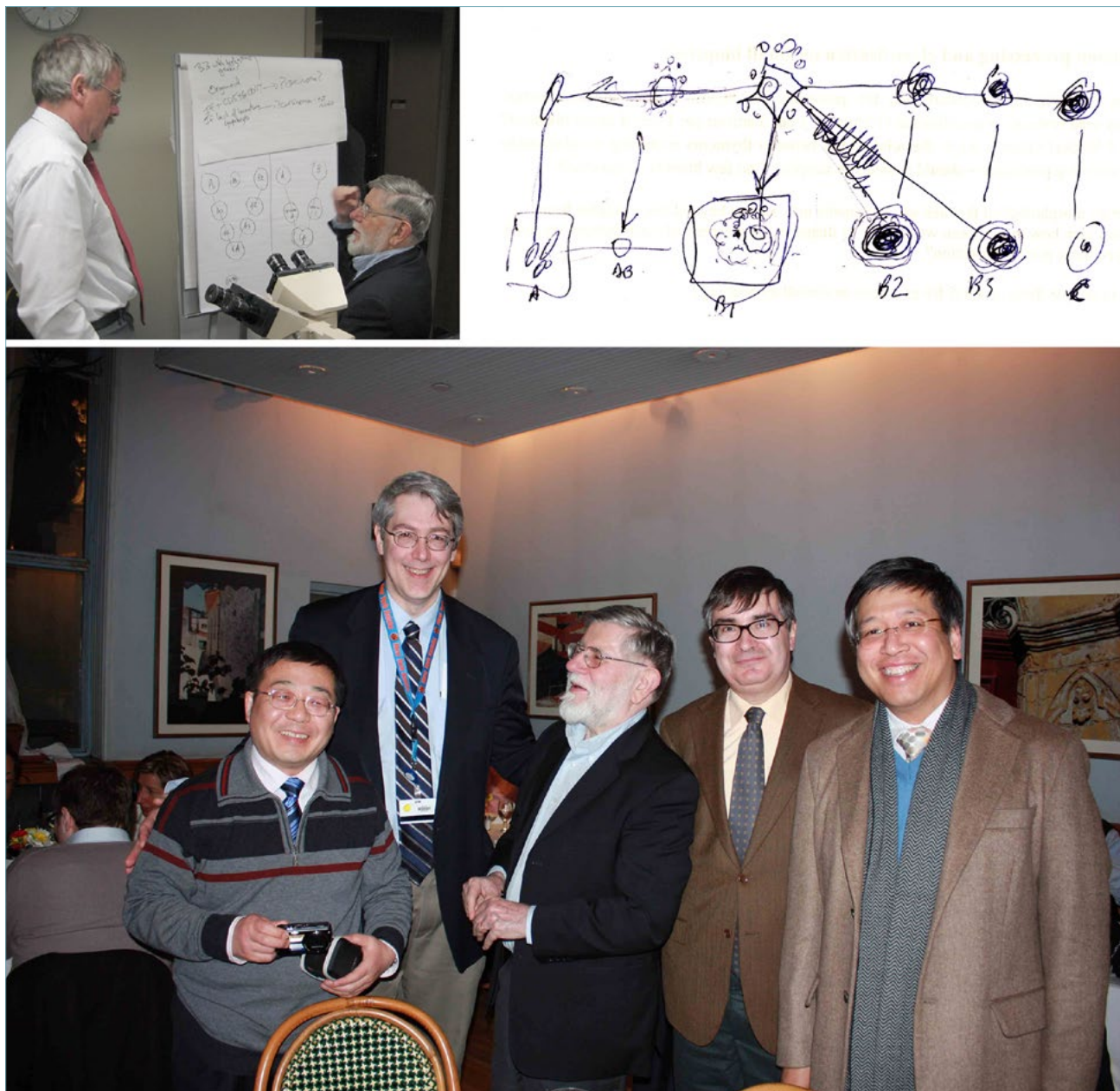
Thymic carcinomas (TC) and thymic neuroendocrine tumors (TNET) are among the rarest tumors of the thymus, and their definition and better understanding as part of Dr. Juan Rosai's legacy also reflects the technical advances of the era with electron microscopy, immunohistochemistry and, later, molecular pathology. The thymus was already known to the ancient greeks: the name and first description of the thymus is attributed to the greek physician Rufus of Ephesus (98-117 AD) who lived in the age of the roman emperor Trajan <sup>1</sup>. However, even though the "father of hematology," William Hewson (1739-1774), correctly assumed that the thymus was a lymphatic organ and even described the phenomenon of lymphocyte export from the thymus into the peripheral blood and the principle of thymic involution <sup>2,3</sup>, it remained an organ with enigmatic structure and function until 1961, when Jaques Miller discovered its role in the production of T cells and its critical role in the immune system <sup>4,5</sup>.

### Dr. Rosai's legacy on the topic thymic carcinomas

The recognition of tumors originating from the thymus and their systematic separation into epithelial and non-epithelial neoplasms required time as well as technical advances and began by the end of the 19<sup>th</sup> century and lasted well into the second half of the 20<sup>th</sup> century. Searching the literature, some examples of putative thymic carcinomas can be traced: in 1894, Ambrosini reported a tumor of the thymus which had involved the lungs and pericardium <sup>6</sup>. The tumor appeared to be a scirrhous carcinoma.

Two years later, in 1886, Paviot and Gerest described a tumor of the thymus in a 52 years old woman which had metastasized to the kidney capsule, regarded by some as the first description of a thymic carcinoma <sup>7</sup>. Their histological description states that the tumor was epithelial, organized in cords and contained spherical bodies derived from the epithelial cells, and showed

an abundant, poorly vascularized stroma. The authors also stressed the significance of these corpuscles in the diagnosis of tumors of the thymus <sup>8</sup>. A few other descriptions of thymic carcinomas can be traced in the literature of the early 20<sup>th</sup> century <sup>9-11</sup>, but the term “thymoma” (first introduced by Grandhomme in 1900) <sup>12</sup> was generally used for all types of neoplastic disorders



**Figure 1.** ITMIG consensus meeting and Dinner in New York 2011. Dr. Rosai in discussion with Dr. Marx over alternative “type A” and “type B” routes of thymoma development. This discussion was continued at dinner. The graph was drawn by Dr. Rosai (the original was actually drawn on a napkin at dinner). Dr. Rosai among other participants of that meeting (from left to right: Drs. Chen Gang, William D. Travis, Ramon Rami-Porta, John KC Chan).

of the anterior mediastinum until the 1970s. Based on careful morphological studies of the thymus and mediastinal tumors published in a series of articles<sup>13-15</sup>, Juan Rosai and Gerald Levine in 1976 wrote the first systematic text book on thymic pathology, the fascicle on thymic lesions in the series of Tumor Atlases by the Armed Forces Institute of Pathology (AFIP)<sup>16,17</sup>. Therein, Rosai and Levine reserved the term thymoma for epithelial tumors and introduced the separation of thymic epithelial tumors (TET) into category I – tumors with no or minimal cytologic atypia (thymoma) and cat-

egory II – cytologically malignant tumors, thereby de facto separating thymic carcinomas from thymomas, although it would require the 2004 edition of the World Health Organization (WHO) classification to finally conclude this distinction by abandoning the term “type C thymoma” for thymic carcinomas. Levine and Rosai described virtually all of the major subtypes of thymic carcinomas known today, namely squamous cell, lymphoepithelioma-like, clear cell, sarcomatoid, and undifferentiated<sup>18</sup>, which were soon completed by basaloid, mucoepidermoid<sup>19</sup>, thymic tumors with adenoid cystic



**Figure 2.** ITMIG slide workshop 2011 in Mannheim. For two days, a panel of expert pathologists reviewed problematic cases that had been selected to illustrate “borderlands”, such as the distinction between some type B3 thymomas with aberrant CD5 expression and thymic carcinomas with immature lymphocytes (see agenda for day 2) in the lower right panel. These discussions were published in an ITMIG consensus paper and formed the basis for the 4th edition of the WHO in 2015. Upper left panel: Dr. Rosai in discussion with Dr. Lauriola.



carcinomalike features<sup>20</sup>, and papillary carcinomas<sup>21</sup>. Together with Dr. Kornstein, Dr. Rosai made the important observation that most thymic carcinomas (in contrast to the vast majority of thymomas) express CD5<sup>22</sup>, which has since greatly helped to distinguish thymomas and thymic carcinomas more safely and to make large international case collections more reproducible and comparable. All major clinical trials and the authoritative molecular study by The Cancer Genome Atlas Program (TCGA) 23 have now confirmed BEYOND DOUBT the initial postulate by Drs. Levine and Rosai that thymic carcinomas should be separated from thymomas and pursue a more aggressive course. Dr. Rosai described the frequent association of papillary carcinomas with “spindle cell thymomas” (now type A or AB thymomas) and discussed their possible relationship to the papillary structures that occur occasionally especially in type A thymomas. This was later an important argument for his provocative theory that there could be an alternative “type A” next to the more common “type B” cancerogenic route that might converge again later in some carcinomas (Fig. 1). Together with a long list of other outstanding pathologists, Dr. Juan Rosai later published some of the largest case collections with clinical annotations of these subtypes<sup>21,24-27</sup>, which essentially contain most of our knowledge about histomorphology and clinical behaviour of these extremely rare tumors up to this day.

As described elsewhere in this fascicle, Dr. Rosai with his undisputed international authority and his ability to highlight the essential strengths and weaknesses of scientific arguments even in heated discussions in an unbiased and open fashion played an eminent role in the reconciliation of the different classification schemes of that time as a basis for the first version of the now uniformly accepted WHO classification system of 1999<sup>28</sup>. Even though the WHO system (revised in 2004) had gained widespread acceptance by 2010 and had shown to reflect the basic biological features and clinical behaviour of TET, it was felt that some of the criteria needed refinement and better definition. To address these issues, an interdisciplinary conference in New York was organized by the International Thymic Malignancy Interest Group (ITMIG) in March 2011 (Fig. 1), followed by a consensus slide workshop in December 2011 in Mannheim (Fig. 2)<sup>29</sup>. Dr. Rosai played a very decisive role on both occasions, sharing many new ideas with much food for thought. One offspring of those meetings was the concept of atypical type A thymoma<sup>30</sup>, which was also included as a provisional variant in the WHO classification of 2015<sup>31</sup>.

## Dr. Rosai’s legacy on the topic (thymic) neuroendocrine tumors

Neuroendocrine tumors were another topic dear to Dr. Juan Rosai. In 1907, Siegfried Oberndorfer introduced the term “carcinoid” for small-cell tumors of the intestines<sup>32,33</sup> and noted that these tumors could occur as single or multiple lesions. The first report of a small-cell tumor (“oat-celled sarcoma”) of the mediastinum was provided in 1926 (actually 10 years before the first description of this tumor in the lung) by W. G. Barnard<sup>34</sup>; carcinoids had been reported even earlier<sup>35</sup>. In fact, it later turned out that the thymus is probably the third most common site of carcinoids, after the intestines and the lung<sup>33,36</sup>. In the 1950s, the existence of oat- or small cell carcinomas (though still under different names) in multiple organs was widely acknowledged<sup>37</sup>, together with a more concise description of its salient histological features<sup>38</sup>. Shortly afterwards, Bensch et al. discovered that oat-cell carcinomas and carcinoid tumors could be traced down to polypeptide hormone producing cells and are histogenetically related<sup>33,39</sup>. The description of an atypical variant of carcinoids by Arrigoni et al. in 1972<sup>40</sup> led Dr. Rosai and colleagues to formulate the concept that there is a spectrum of neuroendocrine neoplasms in which typical carcinoids and small cell carcinomas form the opposite ends<sup>41</sup>.

Dr. Rosai and his colleagues clearly demonstrated that the morphologic, functional, and behavioral characteristics of thymic carcinoids were different from those of thymoma<sup>14,18,41,42</sup> and described the association with MEN1 syndrome<sup>43</sup>. Together with Dr. Lauriola, Dr. Rosai very early clarified that neuroendocrine differentiation in the thymus, similar to most other organs, is not limited to tumors with an identifiable neuroendocrine appearance in hematoxylin-eosin-stained slides, such as carcinoid tumor and small cell carcinoma, but rather that it represents a common event shared by the major types of malignant epithelial tumors of that organ<sup>44</sup>, an important issue that has perhaps not been satisfactorily solved in some other organs until this day. A recent consensus concept has formulated a common classification framework for neuroendocrine neoplasms<sup>45</sup>. The key feature of this new classification is a distinction between differentiated neuroendocrine tumors (NETs) (carcinoid tumors), and poorly differentiated neuroendocrine carcinomas, as they both share common expression of neuroendocrine markers. This dichotomous morphological subdivision into NETs and NECs can also be observed in the thymus by all available histologic, genetic, and clinical differences<sup>46</sup> and goes back to the initial observations of Dr. Rosai and his colleagues.

Another relevant and as yet not fully resolved issue is the relationship of thymic neuroendocrine tumors and

their pulmonary counterparts and neuroendocrine tumors of the gastrointestinal tract. In one of his very characteristic and rather timeless reflections on this subject (half-ironically termed “divagations” by himself), Dr. Rosai argued that “there is [...] a ‘gradient’ of neural as opposed to epithelial features in the system, which relates to topography and which is generally ignored. Thus, the neuroendocrine cells located in the larynx, lung, thymus, and thyroid (C cells) are the most ‘neural-like’ cells of the system, a feature that becomes obvious in the corresponding tumors. [...] Conversely, the (neuro)endocrine cells of the digestive tract and their tumors lack almost always these features (or exhibit them in a very abortive manner) and show instead epithelial-like qualities. Nowhere is this fact more obvious than in the pancreas, where the (neuro)endocrine cells detach from their mucosal companions to be on their own through the formation of the miniendocrine glands known as Langerhans’ islets. It would seem as if the more specialized the cell is concerning its endocrine role, the more epithelial and the less neural it becomes. One would assume that this increasing specialization along epithelial lines in detriment of the neural features is the result of a genetic reprogramming leading to progressive expression of epithelial-type genes coupled with progressive decrease of the expression of neural-type genes”<sup>47</sup>. Thoughts like these, which, in his own words “did not emerge from the results of an ingenious experimental model [...], (but) represent the condensation of life-long reflections [...] based on the many writings on the subject (particularly the early works of master histologists), on random microscopic observations made on routine and consult material, and on discussions held over the years with people who were as fascinated as myself by the subject, guided by the belief that nothing in cell biology is casual, confident that static histology can still teach us something about function, and aware of the fact that pathologic anatomy can throw light on the corresponding normal anatomy” highlight in a nutshell the ingenuity of Dr. Juan Rosai. He was a confident but not obstinate believer in the power of histomorphology<sup>48</sup>, an advocate for the fusion of surgical pathology and basic science<sup>49</sup>. His way of seeing pathology through “Rosai-coloured glasses”<sup>50</sup>, aware both of the past and the future, was ideally illustrated in his description of desmoplastic small round cell tumor<sup>51</sup> which was later on confirmed by the discovery of a specific recurrent gene fusion<sup>52</sup>. His open-mindedness let him anticipate new ideas and technologies long before they became general practice, such as standardized reporting of pathology diagnoses<sup>53</sup>, the detection of circulating tumor cells<sup>54</sup>, or the use of digital slide images for expert consultations across continents<sup>55</sup>.

Dr. Juan Rosai was, in short, not only the doyen of mediastinal pathology, but also one of the most influential pathologists of the 20th century.

## Authors’ contributions

All authors contributed in the conception of the study. AM and PS drafted the manuscript; AM, PS and LDT revised and corrected the paper; LDT submitted the paper and is the corresponding author.

## Ethical consideration

No ethical issue was raised by this work.

## References

- 1 Kirschner PA. The history of surgery of the thymus gland. *Chest Surg Clin N Am* 2000;10:153-165, x.
- 2 Doyle D. William Hewson (1739-74): the father of haematology. *Br J Haematol* 2006;133:375-181. <https://doi.org/10.1111/j.1365-2141.2006.06037.x>
- 3 Lavini C. The Thymus from antiquity to the present day: the history of a mysterious gland, in thymus gland pathology. In: Lavini C, Moran C, Morandi U, et al, eds. *Clinical, diagnostic, and therapeutic features*. Milan: Springer-Verlag Italia 2008.
- 4 Miller JF. Events that led to the discovery of T-cell development and function--a personal recollection. *Tissue Antigens* 2004;63:509-517. <https://doi.org/10.1111/j.0001-2815.2004.00255.x>.
- 5 Miller JF. The golden anniversary of the thymus. *Nat Rev Immunol* 2011;11:489-495. <https://doi.org/10.1038/nri2993>
- 6 Ambrosini G. De l'epithelioma du thymus. *These de Paris*, 1894.
- 7 Marino, M, Roden AC. The evolution of the histopathologic classification of thymic epithelial tumors. *Mediastinum* 2018;2:9. <https://doi.org/10.21037/med.2018.01.04>
- 8 Paviot J, Gerest E. Un cas d'epithelioma primitif du thymus. *Archives de Médecine Expérimentale et d'Anatomie Pathologique* 1896.
- 9 Rubaschow S. Eine bosartige Thymusgeschwulst. *Virchows Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin* 1911;206:141.
- 10 Ewing J. *Neoplastic Diseases*. 2nd ed. Philadelphia: W.B. Saunders 1922.
- 11 Foot NC. Concerning “Malignant Thymoma”; with a report on a case of primary carcinoma of the thymus. *Am J Pathol* 1926;2:33-46.7.
- 12 Grandhomme F. Über Tumoren des vorderen Mediastinums und ihre Beziehungen zu der Thymusdrüse. Heidelberg: Inaug Diss 1900.
- 13 Levine GD, Rosai J, Bearman RM, et al, The fine structure of thymoma, with emphasis on its differential diagnosis. A study of ten cases. *Am J Pathol* 1975;81:49-86.
- 14 Rosai J, Higa E. Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases. *Cancer* 1972;29:1061-1074. [https://doi.org/10.1002/1097-0142\(197204\)29:4<1061::aid-cnrcr2820290456>3.0.co;2-3](https://doi.org/10.1002/1097-0142(197204)29:4<1061::aid-cnrcr2820290456>3.0.co;2-3)
- 15 Levine GD, Bensch KG. Epithelial nature of spindle-cell thymoma. An ultrastructural study. *Cancer* 1972;30:500-511. [https://doi.org/10.1002/1097-0142\(197208\)30:2<500::aid-cnrcr2820300230>3.0.co;2-r](https://doi.org/10.1002/1097-0142(197208)30:2<500::aid-cnrcr2820300230>3.0.co;2-r)

- 16 Wick MR. Mediastinal pathology and the contributions of Dr. Juan Rosai. *Semin Diagn Pathol* 2016;33:319-332. <https://doi.org/10.1053/j.semdp.2016.05.005>
- 17 Rosai J, Levine G. Tumors of the thymus. *Atlas of tumor Pathology*. Washington D.C.: Armed Forces Institute of Pathology, Vol. 13, 1976.
- 18 Levine GD, Rosai J. Thymic hyperplasia and neoplasia: a review of current concepts. *Hum Pathol* 1978;9:495-515. [https://doi.org/10.1016/s0046-8177\(78\)80131-2](https://doi.org/10.1016/s0046-8177(78)80131-2)
- 19 Snover DC, Levine GD, Rosai J. Thymic carcinoma. Five distinctive histological variants. *Am J Surg Pathol* 1982;6:451-470.
- 20 Di Tommaso L, Kuhn E, Kurrer M, et al. Thymic tumor with adenoid cystic carcinomalike features: a clinicopathologic study of 4 cases. *Am J Surg Pathol* 2007;31:1161-1167. <https://doi.org/10.1097/PAS.0b013e3180555ba8>
- 21 Matsuno Y, Morozumi N, Hirohashi S, et al. Papillary carcinoma of the thymus: report of four cases of a new microscopic type of thymic carcinoma. *Am J Surg Pathol* 1998;22:873-880. <https://doi.org/10.1097/0000478-199807000-00009>
- 22 Kornstein MJ, Rosai J. CD5 labeling of thymic carcinomas and other nonlymphoid neoplasms. *Am J Clin Pathol* 1998;109:722-726. <https://doi.org/10.1093/ajcp/109.6.722>
- 23 Radovich M, Pickering CR, Felau I, et al. The Integrated Genomic Landscape of Thymic Epithelial Tumors. *Cancer Cell* 2018;33:244-258.e10. <https://doi.org/10.1016/j.ccell.2018.01.003>
- 24 Suster S, Rosai J. Thymic carcinoma. A clinicopathologic study of 60 cases. *Cancer* 1991;67:1025-1032. [https://doi.org/10.1002/1097-0142\(19910215\)67:4<1025::aid-cncr2820670427>3.0.co;2-f](https://doi.org/10.1002/1097-0142(19910215)67:4<1025::aid-cncr2820670427>3.0.co;2-f)
- 25 Hassserjian RP, Klimstra DS, Rosai J. Carcinoma of the thymus with clear-cell features. Report of eight cases and review of the literature. *Am J Surg Pathol* 1995;19:835-841. <https://doi.org/10.1097/0000478-199507000-00012>
- 26 Nonaka D, Klimstra D, Rosai J. Thymic mucoepidermoid carcinomas: a clinicopathologic study of 10 cases and review of the literature. *Am J Surg Pathol* 2004;28:1526-1531. <https://doi.org/10.1097/01.pas.0000137999.23780.2a>
- 27 Brown JG, Familiari U, Papotti M, et al. Thymic basaloid carcinoma: a clinicopathologic study of 12 cases, with a general discussion of basaloid carcinoma and its relationship with adenoid cystic carcinoma. *Am J Surg Pathol* 2009;33:1113-1124. <https://doi.org/10.1097/PAS.0b013e3181a2443b>
- 28 Rosai J, Sobin LH, eds. *Histological Typing of Tumours of the Thymus*. World Health Organization. International Histological Classification of Tumours. Springer: Berlin, Heidelberg 1999.
- 29 Marx A, Strobel P, Badve SS, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. *J Thorac Oncol* 2014;9:596-611. <https://doi.org/10.1097/JTO.0000000000000154>
- 30 Nonaka D, Rosai J. Is there a spectrum of cytologic atypia in type A thymomas analogous to that seen in type B thymomas? A pilot study of 13 cases. *Am J Surg Pathol* 2012;36:889-894. <https://doi.org/10.1097/PAS.0b013e31824fff50>
- 31 Strobel P, Marx A, Badve SS, et al. Type A thymoma, including atypical variant. In: Travis W, Brambilla E, Burke AP, et al., eds. *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*. Lyon: IARC Press 2011, p. 187-193.
- 32 Oberndorfer S. Karzinoide Tumoren des Dünndarms. *Frankf Z Pathol* 1907;1:426-432.
- 33 Hajdu SI, Tang P. A note from history: the saga of carcinoid and oat-cell carcinoma. *Ann Clin Lab Sci* 2008;38:414-417.
- 34 Barnard W. The nature of the "oat-celled sarcoma" of the mediastinum. *J Pathol Bacteriol* 1926;29:241-244.
- 35 Masson P. *Diagnostic de Laboratoire*. Paris: Maloine 1923.
- 36 Li AF, Hsu HS, Hsu CY, et al. A 20-year retrospective study of small-cell carcinomas in Taiwan. *J Surg Oncol* 2010;102:497-502. <https://doi.org/10.1002/jso.21629>
- 37 Liebow A. *Tumors of the lower respiratory tract*. Washington, DC: A.F.I.o. Pathology 1952.
- 38 Azzopardi J. Oat cell carcinoma of the bronchus. *J Pathol* 1959;513-519.
- 39 Bensch KG, Corrin B, Pariente R, et al. Oat-cell carcinoma of the lung. Its origin and relationship to bronchial carcinoma. *Cancer* 1968;22:1163-1672. [https://doi.org/10.1002/1097-0142\(196811\)22:6<1163::aid-cncr2820220612>3.0.co;2-l](https://doi.org/10.1002/1097-0142(196811)22:6<1163::aid-cncr2820220612>3.0.co;2-l)
- 40 Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg* 1972;64:413-421.
- 41 Rosai J, Levine G, Weber WR, et al. Carcinoid tumors and oat cell carcinomas of the thymus. *Pathol Annu* 1976;11:201-226.
- 42 Wick MR, Rosai J. Neuroendocrine neoplasms of the thymus. *Pathol Res Pract* 1988;183:188-199. [https://doi.org/10.1016/S0344-0338\(88\)80046-3](https://doi.org/10.1016/S0344-0338(88)80046-3)
- 43 Rosai J, Higa E, Davie J. Mediastinal endocrine neoplasm in patients with multiple endocrine adenomatosis. A previously unrecognized association. *Cancer* 1972;29:1075-1083. [https://doi.org/10.1002/1097-0142\(197204\)29:4<1075::aid-cncr2820290457>3.0.co;2-o](https://doi.org/10.1002/1097-0142(197204)29:4<1075::aid-cncr2820290457>3.0.co;2-o)
- 44 Lauriola L, Erlanson RA, Rosai J. Neuroendocrine differentiation is a common feature of thymic carcinoma. *Am J Surg Pathol* 1998;22:1059-1066. <https://doi.org/10.1097/0000478-199809000-00003>
- 45 Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol* 2018;31:1770-1786. Epub 2018 Aug 23. <https://doi.org/10.1038/s41379-018-0110-y>
- 46 Dinter H, Bohnenberger H, Beck J, et al. Molecular classification of neuroendocrine tumors of the thymus. *J Thorac Oncol* 2019;14:1472-1483. Epub 2019 Apr 28. <https://doi.org/10.1016/j.jtho.2019.04.015>
- 47 Rosai J. The origin of neuroendocrine tumors and the neural crest saga. *Mod Pathol* 2011;24Suppl 2:S53-57. <https://doi.org/10.1038/modpathol.2010.166>
- 48 Rosai J. The continuing role of morphology in the molecular age. *Mod Pathol* 2001;14:258-260. <https://doi.org/10.1038/modpathol.3880295>
- 49 Rosai J. Pathology: a historical opportunity. *Am J Pathol* 1997;151:3-6.
- 50 Swanson PE. Diagnostic immunohistochemistry through Rosai-coloured glasses. *Semin Diagn Pathol* 2016;33:343-356. Epub 2016 Jul 19. <https://doi.org/10.1053/j.semdp.2016.07.001>
- 51 Gerald WL, Miller HK, Battifora H, et al. Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. *Am J Surg Pathol* 1991;15:499-513.
- 52 Gerald WL, Rosai J, Ladanyi M. Characterization of the genomic breakpoint and chimeric transcripts in the EWS-WT1 gene fusion of desmoplastic small round cell tumor. *Proc Natl Acad Sci U S A* 1995;92:1028-1032. <https://doi.org/10.1073/pnas.92.4.1028>
- 53 Frable WJ, Kempson RL, Rosai J. Quality assurance and quality control in anatomic pathology: standardization of the surgical pathology report. *Mod Pathol* 1992;5:102a-102b.
- 54 Ghossein RA, Bhattacharya S, Rosai J. Molecular detection of micrometastases and circulating tumor cells in solid tumors. *Clin Cancer Res* 1999;5:1950-1960.
- 55 Eusebi V, Foschini L, Erde S, et al. Transcontinental consults in surgical pathology via the Internet. *Hum Pathol* 1997;28:13-16. [https://doi.org/10.1016/s0046-8177\(97\)90272-0](https://doi.org/10.1016/s0046-8177(97)90272-0)