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Thymic epithelial tumours - research trends

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The global research trends and potential gaps in global research on thymic epithelial tumours (TETs) were scientometrically identified based on the data retrieved from Web of Science (WoS). The analysis indicates that the global research on TETs is presenting a positive growth trend. The transformative activity index (TAI) value depicts that three Asian countries, China, South Korea, and India, recorded the highest increase in TAI during the last decade, while the maximum decline in TAI was for Norway, Taiwan and Netherlands. The University of Texas has published most papers on TETs, and Heidelberg University had the highest collaboration. There is not enough research ongoing on some paraneoplastic disorders associated with TETs like cerebellar degeneration, erythrocytosis, pancytopenia, rheumatoid arthritis, Sjogren's syndrome, interstitial pneumonitis, chronic mucosal candidiasis, T-cell deficiency syndromes, ulcerative colitis, and hypertrophic osteoarthropathy. Most of the TET treatment studies were on surgery and chemotherapy. Research on other treatment modalities like immunotherapy and targeted therapy also needs improvement.

Keywords: Thymic epithelial tumours; Scientometrics; Thymoma; Research trends; Paraneoplastic disorders

Introduction

Thymic epithelial tumours (TET) are comparatively rare thoracic neoplasms originating from the thymus but are the most common anterior mediastinal tumours in adults[1-2]. TETs chiefly include thymomas, thymic carcinomas, and neuroendocrine tumours[3]. TETs are associated with paraneoplastic syndromes, including myasthenia gravis and other immune-mediated syndromes, in up to 45% of cases[4]. The incidence rate of thymoma reported in population studies has ranged from 2.2 to 2.6 per million per year, and that of thymic carcinoma is around 0.3-0.6 per million per year. The data from SEER (Survival, Epidemiology, and End Results) shows that average thymoma incidence rates range from 1.3 to 1.5 million per year but are about three times higher in Asians and Pacific islanders inside USA[3]. The field of thymic tumours suffers from a profound lack of prospective studies, and the few available clinical trials are with limited numbers of patients[5]. As TETs are rare, they are precluded from large phase clinical investigations, and new drugs are slow in development.[6]

Foy et al.[7] analysed Scopus indexed articles and reviews on oral erythroplakia and leukoplakia up to 2016 and concluded that only 4% of oral oncology research was focused on the selected topic and projected that publications might double by 2040. Aggarwal et al.[8] examined the published research on lung cancer by 24 leading countries from 2004 to 2013 using the WoS database. Apart from China, the commitment by most countries to lung cancer research has dwindled. Most lung cancer research was on genetics, systemic therapies, and prognostic biomarkers. Ugolini et al.[9] studied mesothelioma research using scientometrics and noted an association between a country's research commitment and disease burden. The research on pancreatic cancer is constantly progressing, and significant output was from the United States, Germany, and Japan[10]. The USA was in the leading position in both research quantity and quality of triple-negative breast cancer research, and the number of papers from China is rapidly increasing, but the quality of articles still requires improvement[11]. Dwivedi et al.[12] pointed out that the global research output on male breast cancer is growing. Though the publications from China were rapidly increasing, the impact remains less.

The United States topped in quantity and quality of breast cancer research output, and publications with high levels of international cooperation were received more citations[13]. Europe was the most productive continent in eye neoplasm research, followed by

North America and Asia[14]. The global scientific performance on ovarian cancer research is concentrated in few countries, including the USA, UK, China, Germany, Japan, and Italy. Other Asian, South American, and African countries had scant contribution to ovarian cancer research[15]. More than 90 per cent of publications on myeloma were from the USA and European Union, and global multiple myeloma research output has increased significantly in the past decade[16]. There is no exclusive scientometric analysis on thymic epithelial tumours (TET) in the literature.

Objective of the study

- To analyse research trends, geographical distribution, collaboration patterns, identifying the areas of attention, potential gaps, and examine the top-cited papers in global TET research.

Methodology

Data was collected from the core collection of Science Citation Index from Web of Science (WoS) in February 2020 using the following search string formed by referring to "WHO Classification of Tumors of the Lung Pleura Thymus and Heart "[3].

Query: (((((TOPIC: (carcinoma NEAR (thymus OR thymic)) OR TOPIC: (adenocarcinoma NEAR (thymus OR thymic))) OR TOPIC: (carcinoid NEAR (thymus OR thymic))) OR TOPIC: (lipofibroadenomas)) OR TOPIC: (thymoma)) OR TOPIC: ("neuroendocrine tumo*" NEAR (thymus OR thymic))) Timespan: 1945-2019.

The 8732 papers retrieved from WoS were examined manually and selected 6590 publications that discussed any of the TETs or diseases associated with it that are relevant to humans. Papers that discussed TETs in the ectopic positions were excluded. These results were analysed by different quantitative techniques based on scientometrics using Bib-Excel, VOSviewer, and MS Excel.

Results and discussion

Research Growth

The earliest research paper on TET indexed in WoS is the paper titled 'Malignant thymoma' published in 1945 in the *Canadian Medical Association Journal*. Thereafter, the TET research has grown exponentially (Figure 1) in each decade with an R^2 value of 0.98 till 2010. We can see a slight decline in the current decade for the exponential growth with an R^2 value of 0.97. The research papers were cited throughout the period, with an average citation per publication being 20 to 25. In the last five years, more than 300 papers were published every year on TET research.

Geographical Distribution of TET Research

The research on TETs is ongoing in more than 88 countries. Table 1 shows the first ten country's research outputs in different decades and the

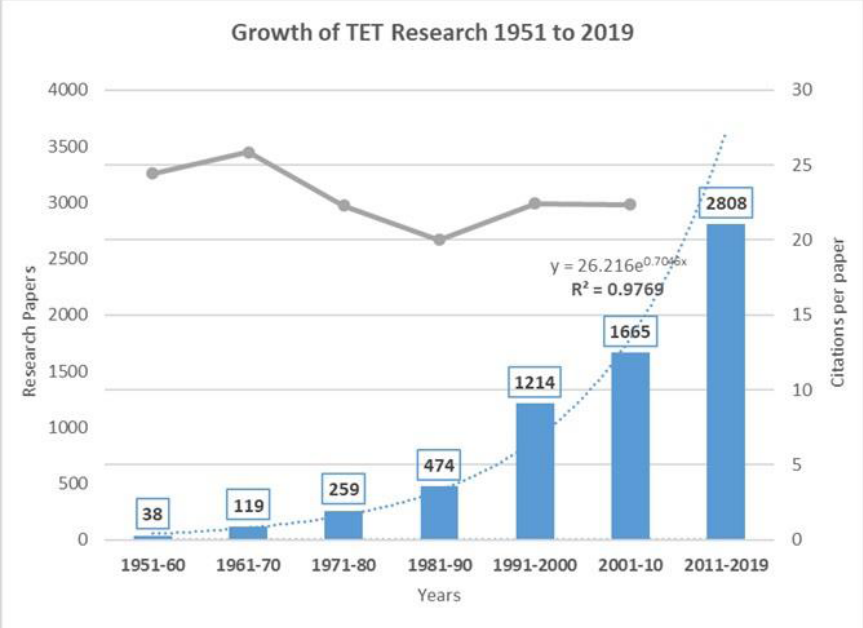

Fig. 1 — Growth of TET Research

Table 1 — Research output and changes in TAIof prolific countries

Rank	Country	Research papers (P)						TAI		Change in TAI
		1972-2019	1972-1979	1980-1989	1990-1999	2000-2009	2010-2019	2000-2009	2010-2019	
1	USA	1608	70	109	255	391	783	100	102	(+)2
2	Japan	1075	6	33	163	307	566	118	111	(-)7
3	Italy	565	4	16	87	149	309	109	115	(+)6
4	P R China	529	1	2	26	41	459	32	182	(+)150
5	Germany	382	11	26	77	96	172	103	95	(-)8
6	UK	331	9	26	60	88	148	109	94	(-)15
7	France	326	14	30	45	78	159	99	102	(+)3
8	South Korea	177	0	0	9	40	128	93	152	(+)59
9	Taiwan	148	0	0	25	60	63	167	89	(-)78
10	Spain	135	6	5	18	38	68	116	106	(-)10
11	Turkey	133	0	0	3	48	82	149	129	(-)20
12	Canada	127	8	11	24	31	53	100	88	(-)12
13	Netherlands	104	1	7	10	37	49	146	99	(-)47
14	India	100	0	0	4	27	69	111	145	(+)34
15	Norway	99	0	7	29	41	22	170	47	(-)123

Table 2 — Citation analysis of top ten institutions

Rank	Institutions	Papers (P)	Total citations (TC)	Citations per paper (CPP)
1	University of Texas, USA	184	4337	23.57
2	Mayo Clinic, USA	121	4590	37.93
3	Memorial Sloan Kettering Cancer Center, USA	116	3689	31.8
4	Nagoya City University, Japan	103	2079	20.18
5	Heidelberg University, Germany	100	2034	20.34
6	Osaka University, Japan	98	2471	25.21
7	National Cancer Center, Japan	86	2016	23.44
8	Indiana University, USA	80	1940	24.25
9	Sapienza University of Rome, Italy	78	1463	18.76
10	University of Bergen, Norway	76	3056	40.21

Transformative Activity Index (TAI). During 1972-79, only 21 countries published on TETs research, and in the next decade (1980-89), it increased to 26 countries. Then more and more countries were involved in research on TETs—45 countries in 1990-99, 64 countries in 2000-09, and 74 countries during 2010-2019. The USA published the highest number of research papers (1608) and showing steady growth over the years, followed by Japan, Italy. Research in South Korea, Taiwan, Turkey, and India started after 1990 and TET research in these countries has grown steadily since 2009.

For analysing the relative change in the output of most prolific countries, we used the Transformative Activity Index (TAI) of Guan and Ma[17], which can be defined mathematically as:

$TAI = [(C_i / C_o)/(W_i / W_o)] \times 100$

C_i is the number of publications of the specific country in the i^{th} block

C_o is the total number of publications of the specific country during the period of study

W_i is the number of publications of all countries in the i^{th} block

W_o is the number of publications of all the countries during the period of the study

Table 1 represents the change in the value of TAI for most productive countries. The TAI value for different countries suggests that TET research growth has increased in the USA, Italy, China, France, South Korea and India during the last decade. Notably, Asian countries like China, South Korea, and India show rapid progress in the past decade. The TAI value of Japan, Germany, the UK, Spain, Turkey, and Canada does not show a positive growth trend. The maximum decline in TAI was noted for Norway, Taiwan and Netherlands, while the highest hike was for China and South Korea.

Prolific institutions in TET research

Four thousand institutions published papers on TET research, but only 435 institutions have published more than five papers during the study period. The ten most prolific institutions responsible for publishing 32% of the total TET research globally are listed in Table 2. The first five institutions have contributed more than 100 papers and together

contributed 10% of the entire TET research. Out of the top ten most prolific organisations, four institutes were from North America (USA), three from Europe (Germany, Norway, and Italy), and three from Asia (Japan). This data shows that TET research is concentrated in a few institutions

Scientific collaboration on TET Research

The high-quality research output comes from collaborative research[18]. International co-authorship was mapped and analysed using the VOSviewer. The USA collaborates with most countries, and the highest collaboration occurred with Italy, resulting in 68 research papers. The partnership between countries in North America and Europe had published most papers, followed by countries within Europe. Japan and China were in the top ten list, and both had published in collaboration with the USA. Among the Asian countries, Japan published most with other countries. Brazil is the only South American country that had collaborative research with North American countries.

Figure 2 shows the multi-institutional collaboration; there are seven major clusters of collaborations; the bubble's size is proportional to the institute's research papers. At the same time, the line width indicates the collaboration strength. Heidelberg University (Germany) had the maximum number of collaborations. University of Texas (USA) has published most papers, and the University of Bergen (Norway) has got the highest number of citations per paper among the top ten institutes.

The only international collaboration amongst the top twenty collaborating institutes occurred between the University of Turin-Italy, and Yale University-USA. The researchers in Haukeland University Hospital and the University of Bergen, both in Norway, have the most number of publications in collaboration (25). Memorial Sloan Kettering Cancer Center-USA (62) was involved in the highest number of partnerships with other institutes.

Prominent journals

The 6590 research papers were published in 1200 journals; however, most research is concentrated in a few journals. The top ten journals are listed in Table 3. The first 25 per cent of the research articles were published in the top one percentage (12)

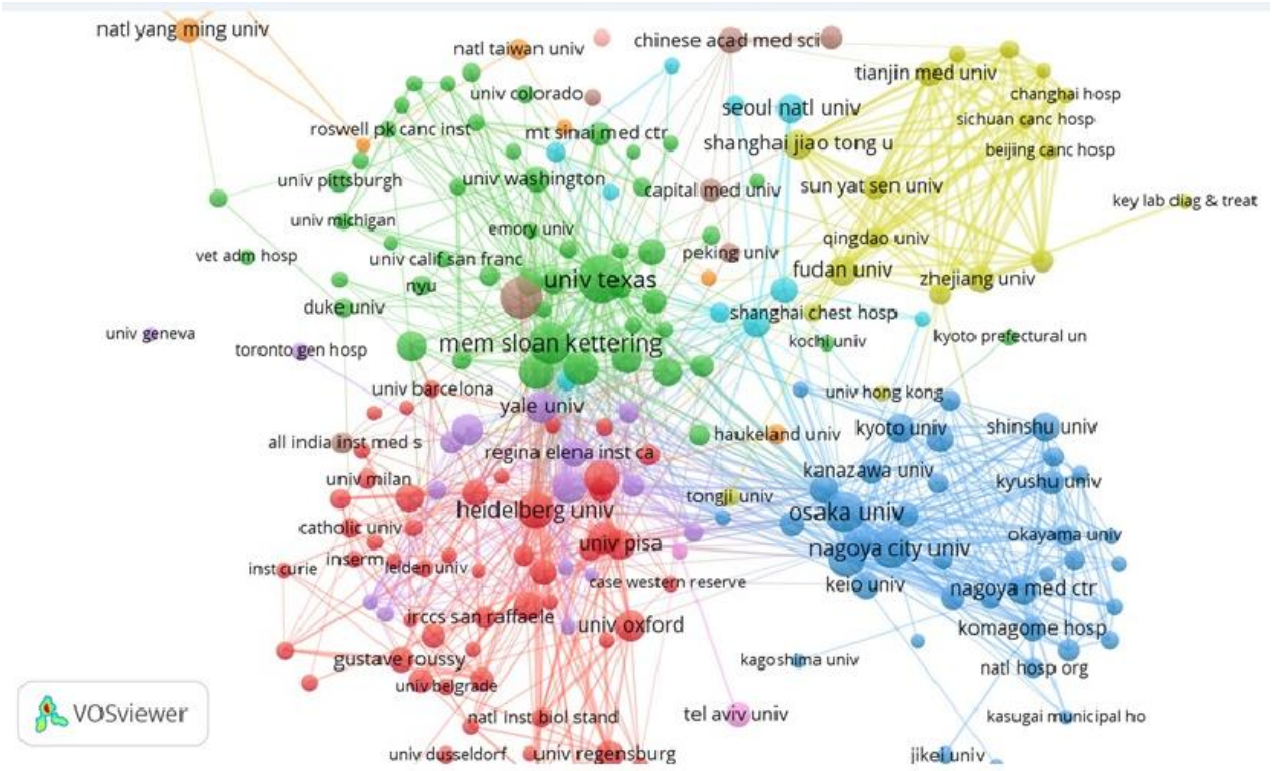

Fig. 2 — Institutional collaboration in TET research

Table 3 — Prominent journals

Rank	Journal	Impact factor (IF 2019)	Papers (P)	Total citations (TC)	Citations per paper(CPP)	Percentage of Not cited Papers
1	*Journal of Thoracic Oncology*	13.357	496	3884	7.83	68.35
2	*Annals of Thoracic Surgery*	3.639	223	6832	30.64	9.42
3	*European Journal of Cardio-Thoracic Surgery*	3.486	123	2051	16.67	14.63
4	*Journal of Thoracic Disease*	2.046	119	357	3.00	35.29
5	*Cancer*	5.742	117	6597	56.38	1.71
6	*Journal of Thoracic and Cardiovascular Surgery*	4.451	90	3408	37.86	12.22
7	*Lung Cancer*	4.702	81	1351	16.68	13.58
8	*Journal of Clinical Oncology*	32.956	78	2214	28.38	35.90
9	*Chest*	8.308	78	1386	17.77	37.18
10	*Laboratory Investigation*	4.197	76	161	2.12	86.84

journals. The first 50% of the articles were published in 5.5% (58) journals. The '*Journal of Thoracic Oncology*' was the most preferred journal with 496 (7%) papers; however, many (68%) of the papers published in this journal are not cited. The publications in the journal '*Annals of Thoracic Surgery*' have received the highest number of citations.

Keyword analysis

Using text analysis, the author keywords were listed and classified based on the treatment, diagnosis, disorders associated with TETs, molecular biology & immunology, prognosis & survival, and staging systems. Keywords with at least three occurrences were selected for keyword analysis.

There were 1474 keywords related to various treatment specialities; of that, the most frequent keyword was surgery (52%), followed by chemotherapy (22%), radiotherapy (11%), immunotherapy (9%), targeted therapy (2%) and other therapies (4%).

Thymectomy was used in 285 papers related to surgical treatment, followed by minimally invasive surgery (MIS) (129). Video-assisted thoracoscopic surgery (58) was the most common keyword in the MIS techniques, followed by robotic surgery (33). Thymectomy may also be performed using MIS[19]. However, only a few papers had discussed thymomectomy(17).

Thymic tumours are responsive to chemotherapy, and the chemotherapy in combination with cisplatin proved to be most effective[20]. Among the chemotherapy drugs discussed, cisplatin was in the first position (23), followed by paclitaxel (17) and carboplatin (11). Platinum-based chemotherapy has been using as the first-line treatment for patients with advanced or metastatic TETs[21]. However, the studies on platinum-based chemotherapy were only seven.

Immunosuppressive therapy has been reported to be useful for thymoma-associated secondary pure red cell aplasia[22]. The most commonly used immunosuppressants are cyclosporine A, tacrolimus, rapamycin and its synthetic derivative everolimus, corticosteroids, azathioprine, and mycophenolate mofetil[23]. There were 132 keywords related to immunotherapy. Among the immunosuppressants, corticosteroids (29) stood first, followed by cyclosporine (13), tacrolimus (10), and cyclosporine A (9). Radiotherapy was in 161, and targeted therapy was discussed in 36 papers. Sunitinib (12) was the widely used drug for targeted therapy. Sixty-two publications dealt with other treatment approaches, of that only a negligible number of studies on proton therapy (3).

We classified the 1351 keywords related to TET associated paraneoplastic disorders with the help of the European Society for Medical Oncology (ESMO) clinical practice guidelines[24].

Paraneoplastic neuromuscular diseases (900) were the most discussed TET associated disorder, followed by immune deficiency disorders (132). Among the neuromuscular diseases, a substantial part (727) was myasthenia gravis (MG), followed by neuromyotonia (40) and encephalitis (34). Good syndrome (Hypogammaglobulinaemia) was the most discussed immune deficiency disorder; however, T-cell deficiency syndrome has not received enough attention.

Among the paraneoplastic haematological disorders (94 keywords), a significant portion was on pure red cell aplasia (58), followed by aplastic anaemia (10). Other TET-associated haematological disorders like pancytopenia, erythrocytosis, and pernicious anaemia, have not obtained adequate consideration. Paraneoplastic endocrine disorders were included in 87 papers; Cushing's syndrome (53) was the most discussed endocrine disorder, followed by multiple endocrine neoplasias (31). Paraneoplastic dermatological disorders were covered only in 24 papers, and pemphigus (16) was the most studied.

Another paraneoplastic dermatological disorder, chronic mucosal candidiasis, has not received sufficient attention. The systemic lupus erythematosus (19) and scleroderma (4), which are collagen and autoimmune disorders, were discussed only in a few studies. The rest of the diseases classified under miscellaneous paraneoplastic syndromes, nephrotic syndrome (24), and superior vena cava syndrome (19) were the most discussed.

A few studies reported a higher risk of cancer for thymoma patients[25-26]. Lymphomas (50) were the most discussed neoplasm that was discussed in TET papers, followed by lung cancer (38) and leukaemia (10). Breast cancer and prostate cancer were discussed in five, and oesophagal cancer was included in three papers. Other cancers were discussed only in very few publications.

Areas in immunology and molecular biology were discussed in 321 papers. Among that, 61 were on autoantibodies, followed by T cells (27). Prognosis of the disease was involved in 182 papers, survival in 76, and the disease's recurrence was discussed in 68 studies. There are around 15 stage classification systems for thymic tumours; the Masaoka-Koga classification system is the commonly used clinical staging system[27-28].

TETs for the first time were included in the TNM staging system because of the joint effort of the International Thymic Malignancy Interest Group (ITMIG), the International Association for the Study of Lung Cancer (IASLC), and the contribution of several important databases[29-30]. The classification and staging systems of TETs were discussed in 111 papers. Masaoka staging system (40%) was the most used, followed by WHO classification (29%). Though TNM classification for TETs has started recently, it was the third most discussed classification system (13%); this indicates that TNM classification will be the most important system in the future for staging TETs.

Keywords are also classified based on their use in the diagnosis of TETs. Diagnosis is again classified into pathology (35%), medical imaging tests (29%), biomarkers (12%), and other diagnostic techniques (25%). There were 253 papers related to pathology; 64% (161) of those were related to immunohistochemistry. Titin antibodies are using to detect thymoma in MG patients and may serve as biomarkers to monitor therapeutic responses[31]. Eighty-four papers discussed biomarkers; titin antibodies (23) was the most discussed biomarker, followed by C-KIT (12). Diagnostic imaging was discussed in 204 studies. Computed tomography (CT) was the most used imaging test (46%), followed by positron emission tomography (PET) (24%), magnetic resonance imaging (12%), and PET-CT (8%). Positron emission tomography (PET) scan using fluorine18 fluorodeoxyglucose (FDG) is a powerful tool for diagnosing, staging and restaging several malignancies, including TETs[32-33]. By analysing keywords, it can be found that PET is also emerging as one of the critical tools involved in the studies on TETs. Amongst the 180 keywords about the other diagnostic techniques, the anti-acetylcholine receptor antibody was included in 80 papers, followed by thoracoscopy (23).

We examined the title and abstract of papers regarding the average publication year to understand the active research topics. The topics with an average publication year greater than 2014 were considered as TET active research areas. The important topics were anthracycline, gemcitabine, capecitabine, temozolomide, pembrolizumab, Masaoka-koga staging, intensity-modulated radiation therapy, proton therapy, receiver operating characteristic curve, the area under the curve, programmed cell death-ligand-1, international thymic malignancy interest group, and the myasthenia gravis foundation of America.

The topics on which research has tapered off are analysed from words with an average publication year less than 2001. This list includes erythro-blastopenia, pancytopenia, giant cell myocarditis, chronic mucocutaneous candidiasis, lymphocytosis, agranulocytosis, peripheral neuropathy, polymyositis, and Muller hermelink classification. Paraneoplastic disorders included in this list, such as pancytopenia, giant cell myocarditis, and polymyositis, are included in the list of autoimmune disorders in ESMO clinical practice guidelines for TETs 2015[24].

The overlay visualisation of the title word analysis is given in Figure 3. From the analysis, it can be seen that the research focus, in the beginning, was malignant thymoma and MG, then thymic carcinoids. Some of the paraneoplastic disorders like myocarditis, paraneoplastic autoimmune hematologic, and endocrine disorders were the later leading TET research areas. Afterwards, antibodies, including titin antibodies, acetylcholine receptor antibodies, and autoantibodies, have received sufficient attention

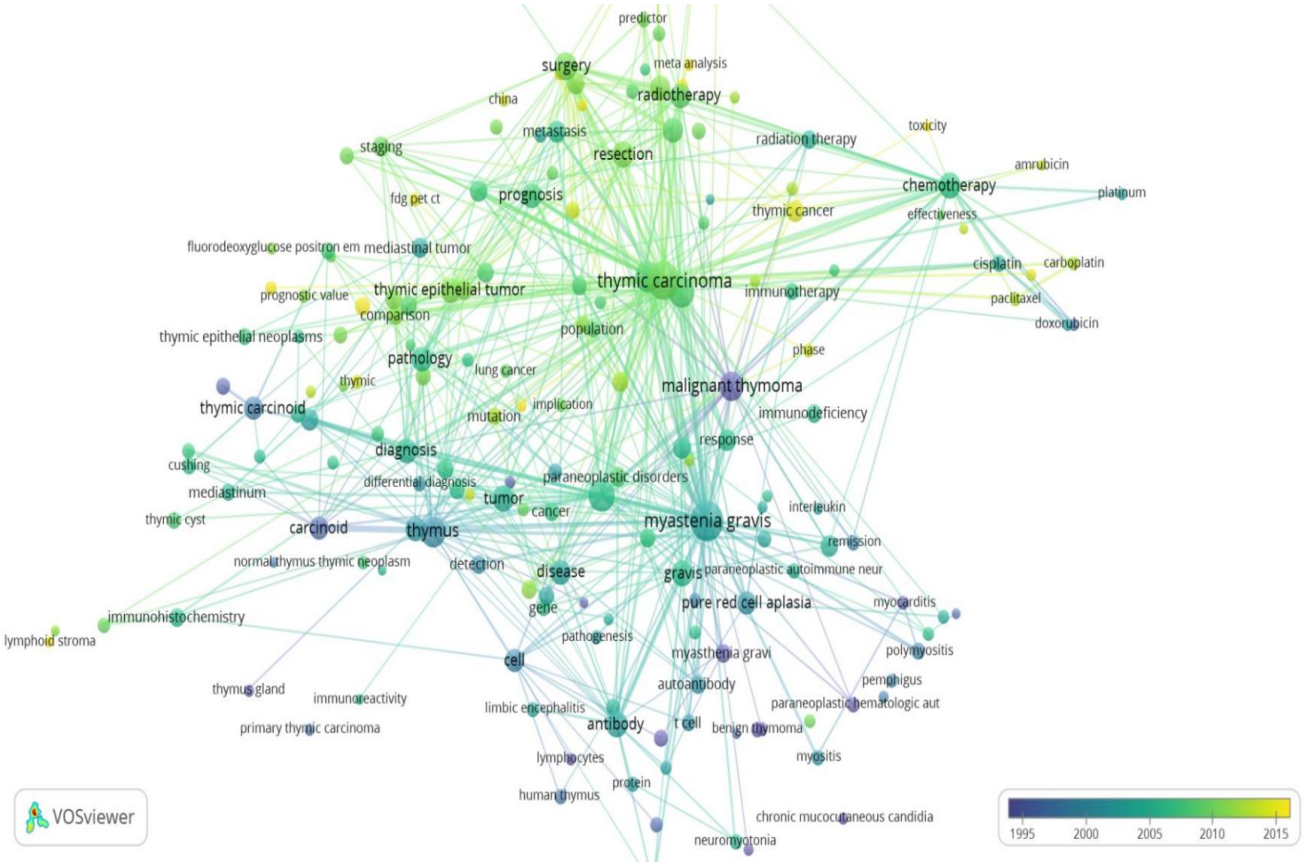

Fig. 3 — Text analysis: Overlay visualisation

from researchers. Then the thymic carcinoma, neuroendocrine tumours, biopsies, staging, classification of tumours, and treatment methods like radiotherapy and chemotherapy (cisplatin, doxorubicin, and cyclophosphamide) had gained adequate attention. Subsequently, NUT carcinoma, immunotherapy, epidemiology, and imaging techniques like computed tomography (CT) and magnetic resonance imaging were active research areas. In recent years, programmed cell death-ligand-1, MIS, PET (including FDG PET), and medicines involving amrubicin, capecitabine (chemotherapeutic drugs), and sunitinib, that is used for targeted cancer therapy were the latest core areas of TET research. Notably, most paraneoplastic disorders are not the current vital areas of research. The title text analysis also reveals that the study on paraneoplastic disorders associated with TET shows negative growth.

Most cited papers

The Review paper on 'Myasthenia gravis - recommendations for clinical research standards'[34] published by a group of authors from Myasthenia Gravis Foundation of America in 2000 in the journal Neurology has been cited 702 times (citation data: May 5, 2020). The top three highly cited papers[34-36] that have been cited more than six hundred times are related to the paraneoplastic syndromes associated with TETs. The first and third most cited publications are review papers.

Top cited papers published within the last five years

Table 4 lists the highly cited papers published in the past five years. As in the top-cited paper list, the most cited paper (240 citations) within the last five years is also on MG. Unlike the titles in the list of highly cited papers, it can be observed that some topics like eculizumab (immunotherapy drug), sunitinib (used for targeted therapy), and programmed cell death-ligand 1 (used for immunotherapy and as a marker for tumour prognosis) have emerged in the titles of the recent top-cited papers.

Table 4 — Top cited recent papers (citation data on May 5, 2020)

Sl No	Title of research paper	Journal	Document type	Citations	Publication year
1	Myasthenia gravis: subgroup classification and therapeutic strategies	*Lancet Neurology*	Review	240	2015
2	The 2015 World Health Organization Classification of Tumors of the Thymus Continuity and Changes	*Journal of Thoracic Oncology*	Review	130	2015
3	Encephalitis and AMPA receptor antibodies Novel findings in a case series of 22 patients	*Neurology*	Article	107	2015
4	Myasthenia gravis - autoantibody characteristics and their implications for therapy	*Nature Reviews Neurology*	Review	91	2016
5	Thymic carcinoma outcomes and prognosis: Results of an international analysis	*Journal of Thoracic and Cardiovascular Surgery*	Article	85	2015
6	The Caspr2 antibody-associated disease	*Neurology*	Article	83	2016
7	Thymic epithelial tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (aEuro)	*Annals of Oncology*	Article	81	2015
8	Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial	*Lancet Oncology*	Article	78	2015
9	Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study	*Lancet Neurology*	Article	75	2017
10	Immunohistochemical status of PD-L1 in thymoma and thymic carcinoma I	*Lung Cancer*	Article	75	2015

Conclusion

Based on the available epidemiologic data, Asians and Pacific islanders have a higher rate of thymoma[3]. The transformative activity index data suggests that the research on TET is rapidly increasing in some Asian countries, including China, South Korea, and India. TET treatment requires a multidisciplinary approach as the multidisciplinary treatment approach has proved to be more effective for TETs[37]. However, 74% of the studies on TET treatment were on surgery and chemotherapy; hence the research on other treatment modalities like immunotherapy, targeted therapy needs to be improved. Anthracycline, amrubicin, gemcitabine, capecitabine, temozolomide, sunitinib, and pembrolizumab were the most discussed medicines by TET for better patient care and management.

Nearly 25 to 40% of thymoma patients have MG, and 15% of thymoma patients having paraneoplastic diseases other than MG[38-39]. It is observed from this study that there is not enough research ongoing on some paraneoplastic disorders associated with TETs like cerebellar degeneration, erythrocytosis, pancytopenia, rheumatoid arthritis, Sjogren's syndrome, interstitial pneumonitis, chronic mucosal candidiasis, T-cell deficiency syndromes, ulcerative colitis, and hypertrophic osteoarthropathy. The research on erythroblastopenia, giant cell myocarditis, lymphocytosis, agranulocytosis, peripheral neuropathy, and polymyositis decreases over the past years. This study points out that the global research on TET is steadily increasing, though the researchers need to focus more on the rare paraneoplastic disorders associated with TETs for better patient care and manegment.

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