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REVIEW

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Prognostic factors and genetic markers in thymic epithelial tumors: A narrative review

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Abstract

Thymic epithelial tumors (TET) are a group of rare neoplasms of the anterior mediastinum comprising thymomas and thymic carcinomas. The carcinogenesis of TET is mostly unknown. Many studies, mostly retrospective case series, have tried to establish prognostic factors in TET. TET is a very heterogeneous group of tumors with many subtypes for which diagnosis and treatment remains a very challenging task. Despite the disparities among retrospective studies, there are some prognostic factors that are more pertinent such as the completeness of resection, TNM stage and the Masaoka-Koga classification. On the other hand, the identification of different genetic pathways that result in the pathogenesis of TET represents a fascinating field of study that could possibly lead to the development of new targeted therapies. The aim of this review is to discuss the different prognostic factors and genetic markers of TET. The meticulous use of national and international databases could provide sufficient number of patients in order to draw more valid conclusions.

KEYWORDS

genetic markers, prognostic factors, thymic carcinoma, thymoma

INTRODUCTION

Thymic epithelial tumors (TET) are a group of rare neoplasms of the anterior mediastinum comprising thymomas and thymic carcinomas.[1] They originate from the epithelial cells of the thymus. Thymomas are indeed the most frequent neoplasms of the prevascular mediastinum. On the other hand, thymic carcinomas account for 15%–20% of all thymic neoplasms.[1] These rare neoplasms (annual incidence 0.15 cases per 100 000) have an indolent course and despite the fact that for many years some of them were considered benign lesions, nowadays they are recognized as malignant neoplasms with sometimes a highly aggressive and metastatic potential.[2] In particular, thymic carcinoma is a highly atypical neoplasm that tends to invade adjacent tissues and metastasize. Consequently, it has a poorer prognosis (5-year survival rate 30%–50%) than thymomas.[2] Many studies, mostly retrospective case series, tried to establish prognostic factors in TET.[3–5] Due to the heterogeneity of resected TET (rarity of the lesion together with many different histological types) there is no consensus and reproducibility of findings. TET can be associated with autoimmune diseases. Myasthenia gravis (MG) is the most common among them (23%–47% of cases). Other autoimmune diseases are red cell aplasia, hypogammaglobulinemia (Good's syndrome), systemic lupus erythematosus, polymyositis, thyroiditis, lichen planus and other rare diseases.[6]

Many staging classification systems have been proposed and applied. The Masaoka staging system (1981) and its modification by Koga (1994) is the most widely used (Table 1).[7–9] The histological classification proposed by the WHO (1999) has been adopted worldwide (Table 2).[8,10,11] Nevertheless, there is no direct correlation between the WHO histological classification and the Masaoka-Koga stage classification.[7–11] In 2014 a new TNM staging system was introduced by the IASLC and the ITMIG (Tables 3 and 4).[12] By using a TNM system, thymic malignancies were thus aligned to other solid cancers.

TABLE 1 The Masaoka-Koga staging system[7,8]

I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
IIb	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)
IVa	Pleural or pericardial metastases
IVb	Lymphogenous or hematogenous metastasis

TABLE 2 The 2015 WHO classification of tumors of the thymus (simplified version concerning the epithelial tumors)[10]

Thymoma
Type A thymoma, including atypical variant
Type AB thymoma
Type B1 thymoma
Type B2 thymoma
Type B3 thymoma
Micronodular thymoma with lymphoid stroma
Metaplastic thymoma
Other rare thymomas
Thymic carcinoma
Squamous cell carcinoma
Basaloid carcinoma
Mucoepidermoid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Sarcomatoid carcinoma

The aim of this review article is to discuss the different prognostic factors and genetic markers of TET and to point out discrepancies and similarities among the available literature (concerning prognostic factors) and more importantly to demonstrate the genetic pathways that could be the basis of a development of new targeted therapies.

METHODS - SEARCH STRATEGY

This article was designed according to the recent recommendations on quality assessment of narrative review articles.[13] Our review article was focused on the two selected elements concerning TET. PubMed research was conducted using the terms [prognostic factors] AND [thymic epithelial tumors] OR [thymomas] and [genetic markers] AND [thymic epithelial tumors] OR [thymomas]. Papers concerning pediatric cases and non-English literature papers were excluded. Since the present study is not a systematic review, the papers were selected according to pertinence. The majority of studies were retrospective cases series and consequently papers with higher level of evidence have not been identified. Among the papers dealing with genetic alterations in thymic tumors, priority was given to recent ones. The references of selected papers were sought in order to find other pertinent articles.

TABLE 3 IASLC/TNM staging system for thymic malignancy[12]

T1	a: Encapsulated or unencapsulated, with or without extension into mediastinal fat b: Extension into mediastinal pleura
T2	Pericardium
T3	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	a: Separate pleural or pericardial nodule (s) b: Pulmonary intraparenchymal nodule or distant organ metastasis

TABLE 4 Stage grouping according to the IASLC/TNM staging system[12]

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIa	T3	N0	M0
IIIb	T4	N0	M0
IVa	T any	N1	M0
	T any	N0, 1	M1a
IVb	T any	N2	M0, 1a
	T any	N any	M1b

Prognostic factors

As already mentioned, the body of evidence concerning the prognostic factors is mainly provided by retrospective studies. The innate heterogeneity of these tumors and the variable proportion of different histological types in each cohort results in discrepancies. However, there are some prognostic factors that consistently appear in almost every study.

Age

A retrospective study enrolling 100 patients suggested that patients aged more than 60 years old have a poorer prognosis than their younger counterparts.[14,15] Yano et al. and Zhao et al. came to the same conclusion in their retrospective studies.[16,17] However, these papers do not clarify if the higher mortality is tumor-related or the results of comorbidities in the elderly.[3]

Sex

Available data show that there is no influence of sex in the prognosis of patients with TET.[14,18]

Presence of myasthenia gravis (MG)

There is controversy over the impact of MG in patients with TET.[19–23] There are studies showing a worse overall survival (OS) in the presence of MG while others do not show any association.[19,23] However, the exact mechanism that results in worse prognosis in the presence of MG is largely unknown.[18,24]

According to some studies, myasthenia gravis does not affect survival in patients with TET.[14,15,25] On the other hand, there are studies suggesting that the presence of myasthenia gravis has a positive impact on survival.[3] A possible explanation according to Wilkins et al. is the fact that MG symptoms lead to the diagnosis of thymomas at an earlier stage. Furthermore, steroids may lead to involution of recurrent thymomas, preventing small recurrences to further develop.

However, it seems that the number of cases in the different cohorts may play a role in the discrepancy concerning the possible role of MG in the survival of patients with TET.[4]

Presence of other autoimmune diseases

A retrospective study of a national database of resected thymomas concluded that the presence of an autoimmune disease other than MG did not significantly influence survival.[26] However, it has been reported that pure red cell aplasia is associated with more advanced thymomas and worse prognosis.[5,26]

Histological type

The WHO histological classification (thymomas vs. thymic carcinomas) is a predicting factor for survival. In general, thymomas have a better prognosis than thymic carcinomas.[27,28] In one study, 5-year survival rates for thymoma and thymic carcinoma were 90 and 75%, respectively and there was a statistically significant difference between these two groups.[27] More specifically, 5-year survival rates in A, AB, B1, B2, B3 types, and thymic carcinomas were 90, 100, 75, 100, 100 and 75%, respectively. Disease-free survival (DFS) among the different histological types was 100, 83, 75, 63, 67 and 80% respectively.[27] In another study, 10-year survival rate was 100% for patients with subtype A tumor, 90% for subtype AB, 78% for subtype B1, 33% for subtype B2, 35% for subtype B3 and 0% for thymic carcinomas.[28] Similarly, in the series of Rioja et al., 83 TET were treated over a 22-year period. Advanced histological WHO types were associated with worse prognosis (OS 16.7 months for B2, B3 types and 12.3 months for thymic carcinomas).[29]

Masaoka-Koga stage

There is robust and reproducible data derived from the available studies demonstrating that an advanced Masaoka-Koga stage is associated with a worst prognosis.[24,25,27–30] In one study, the 5-year OS rates of stage II, III, and IV were 88, 100, and 80%, respectively and 5-year DFS rates were 88, 75, and 55%, respectively.[27] In another study, the 5-year survival rates were 100, 100, 80 and 0%, respectively.[30] As already mentioned, the different proportions of each histological type in the available series could explain the discrepancies in the survival rates, nevertheless there is a clear correlation between advanced stages and worse prognosis. In the series by Rioja et al., advanced Masaoka-Koga stages (III and IV) were a poor prognostic factor (OS 16 months).[29]

TNM stage

In this new classification system (2014), the T component corresponds to tumor invasiveness and not to tumor size. The broader definition of stage I in the TNM system (including tumors that are encapsulated or not, tumors with or without extension into the mediastinal fat and pleura) results in downstaging of patients with Masaoka-Koga stage II tumors. In a retrospective study analyzing 245 patients with resected thymomas, a correlation was found between TNM classification system and WHO histological classification.[31] More specifically, median survival time (MST) was 187 months in Masaoka-Koga stage I, 166 months in stage IIa, 58 months in stage IIb; 107 months in stage III and 53 months in stage IVa respectively. On the other hand, MST was 166 months in TNM stage I, 107 months in stage II, 108 months in stage IIIA, 22 months in stage IIIB, and 98 months in stage IVa. In addition, according to the authors, advanced TNM stages corresponded to more aggressive histologies.[31] Another retrospective study enrolling 154 patients showed that after applying the new classification system the recurrence-free survival rates decreased significantly (HR 2.68 for stage II, 6.84 for stage IIIA, 379.11 for stage IIIB, 8.46 for stage IVA and 24.62 for stage IVB) with increasing stage.[32]

Surgical margins - radicality of excision

Complete excision of the tumor with negative surgical margins is the mainstay of treatment and the best prognostic factor in thymomas, according to the majority of the studies.[8,10,14,25] On the contrary, there is no survival benefit of cytoreductive surgery (debulking), especially in cases of thymic carcinoma that are known to follow a more aggressive course.[33] Surgical debulking is proposed in order to decrease the tumor size in large and inoperable tumors. This will give the opportunity to adapt the external radiation therapy and diminish the side effects of extensive irradiation.[33] However, there is no sufficient data to support the routine use of this strategy.

Lymph node metastasis

A best evidence topic reviewing nine studies was published in 2014 underlining the clinical relevance and prognosis of prevascular (anterior mediastinal) and intrathoracic lymph nodes in TET.[34] According to the authors, a complete lymphadenectomy should be adapted in the surgical treatment of TET. A retrospective analysis of a Chinese database including 1617 patients showed that the incidence of nodal involvement was 2.2% and associated with worse OS.[35] Nodal involvement was found in only seven of 1310 (0.5%) patients with thymoma, whereas in patients with thymic carcinoma and neuroendocrine thymic tumors (NETTs), this involvement was 7.9 and 16.7%, respectively.[35] In general, nodal involvement is more frequent in thymic carcinomas compared to thymomas.[34] In the study conducted by Kondo and Monden (cohort of 1320 patients), thymomas presented nodal involvement in 1.8% of cases, carcinomas in 27%, and carcinoids in 28%. In thymoma patients, a significant difference in 5-year survival was identified between N− and N + patients, without any difference between N1 and N2 stage in the positive cases. A significant difference in 5-year survival according to nodal involvement was observed in carcinomas and NETTs (N0 56.0%; N1 42.1%, N2 29.3%, N3 18.8%).[34,36] Fang et al. observed a rate of lymph node metastasis that was 2.1% in patients with thymomas, 25% in those with thymic carcinomas, and 50% in those with NETTs.[37] Additionally, the authors identified the following predictive factors of nodal involvement: histological WHO type B3, thymic carcinoma, NETT, advanced clinical stages (T3-4) and N2 node dissection. Consequently, they suggest that lymph node dissection should be recommended in these cases, with the addition of ipsilateral N2 nodes. On the contrary, bilateral dissection is usually unnecessary, except for cases of neuroendocrine tumors that present a high prevalence of extensive nodal disease.

Neutrophil-to-lymphocyte ratio (NLR)

The NLR is a surrogate marker of inflammation and plays an important role in cancer growth.[38–41] The NLR is defined as the absolute number of neutrophils divided by the absolute number of lymphocytes in blood samples. An increase in neutrophils or decrease in lymphocytes can activate or deactivate crucial pathways of cancerogenesis related to the action of immune killer cells.[38–42] It has been suggested that high preoperative NLR is associated with shorter DFS in patients with resected TET.[38–41] This novel marker is applicable to other solid tumors, such as mesothelioma, pancreatic cancer, renal cell carcinoma, colorectal carcinoma, gastroesophageal cancer, non-small cell lung cancer, and cholangiocarcinoma etc., yet more data is needed in order to establish its relevance as a prognostic factor in TET.[42]

Localization of the tumor

A retrospective study enrolling 194 patients demonstrated a worse OS and higher recurrence rates in TET located in the superior mediastinum. The limit separating the superior from the inferior mediastinum was set at the level of the sternal angle. However, this distinction is currently not used.[43] It has previously been suggested that the proximity of the tumor to the large vessels in the superior mediastinum could give rise to hematogenous spread.[18]

Performance of extended thymectomy

Extended thymectomy has previously been reported to provide better survival than partial thymectomy (thymomectomy).[17,25,44] In a study by Kamata et al., the 5-year OS rates for thymectomy and extended thymectomy were 100 and 95%, respectively, and recurrence-free survival rates 100 and 80%, respectively. However, the extent of resection is not clearly mentioned in the various series, making comparison difficult. Even if the surgical access has evolved with the introduction of minimally invasive procedures, the optimal surgical strategy remains a subject of debate.[45]

Recurrence-free period

Patients with thymomas who have a recurrence-free period of less than 3 years have a poorer prognosis.[25]

Resection of a recurrence

A retrospective study enrolling 108 patients with TET demonstrated that complete resection of a recurrence provides better survival in comparison with patients receiving other treatments (chemotherapy only or chemoradiotherapy).[28]

Number of recurrent lesions

A small number of recurrent lesions (≤2) detected on computed tomography has been reported to be associated with better prognosis compared to the presence of more lesions.[16]

SUVmax and SUVmax ratio

There appears to be a correlation between the standard uptake value (SUVmax) of TET and the histological type according to the WHO classification and the stage according to the Masaoka-Koga classification.[14,46] Thymic carcinomas can be distinguished from thymomas because of a significantly higher SUVmax. Studies trying to correlate the ratio of the SUVmax of the lesion to the SUVmax of the adjacent

mediastinal tissues (SUVmax ratio) with the invasive nature of TET have been performed.[46] In a study which enrolled 30 patients more advanced Masaoka-Koga stages were observed (without reaching statistical significance) and the capsular invasion was significantly higher when the SUVmax ratio was superior to 1.[46]

Genetic markers

The genetic profile of TET represents a highly heterogeneous, but fascinating, field. There is increasing interest among researchers to establish a genetic profile and the oncogenic driver alterations in the TET that can lead to the development of molecular targeted therapies.[47–49] To date, there has been rather limited progress in this field for the TET, especially in comparison with other solid tumors.

Meng et al. investigated the gene expression profile of eight patients with thymomas and compared them to four patients with thymic cysts.[47] *PLK5* presented the most elevated expression followed by *HMGA2* and *REG4* compared to the control group. These genes are known to introduce oncogenesis and are present in other solid tumors, as well as in leukemias.[47] On the other hand, the tumor suppressor genes *SFRP1*, *CXCL14 and CAVI* present lower expression in thymoma patients.

Petrini et al. identified a mutation at the chromosome 7 c.74146970T > A of the *GTF2I* gene in type A thymomas. In a series of 274 TET, they detected the *GTF2I* mutation in 82% of type A and 74% of type AB thymomas. This mutation correlated with better survival.[48] In general, thymic carcinomas carry a higher number of mutations than thymomas. Recurrent mutations of *Tp53*, *CYLD*, *CDKN2A*, *BAP1* and *PBRM1* have been identified in thymic carcinomas.[48] Alberobello et al. identified alterations of PI3K due to mutations in its catalytic or regulatory subunits in thymic carcinomas.[49]

Schirosi et al. investigated the expression and mutation of the proto-oncogene *cKIT* in thymic carcinomas.[50] The majority of tumors analyzed expressed *CD117* on immunohistochemistry (IHC), while 12.5% of the *CD117* IHC-positive tumors presented a *cKIT* mutation. On the contrary, no mutation was demonstrated in the *CD117* IHC-negative tumors. This is an interesting finding given that tumors harboring a *cKIT* mutation can be targeted with *cKIT* inhibitors. It should be noted that thymomas do not express *CD117* on IHC and do not present with *cKIT* mutation.

Girard et al. analyzed 90 thymomas and 174 thymic carcinomas that were clinically advanced and refractory to the standard treatment in cases of recurrent disease.[51] In this study, the authors found that 10% of the thymomas showed genetic alterations in the *CDKN2A/B* and *TP53* genes. It is noteworthy that an amplification in the *NTRK1* gene was detected in an unresectable stage III type B3 thymoma. However, genetic alterations are more frequent in thymic carcinomas, particularly in squamous, undifferentiated and neuroendocrine carcinomas, and mostly involve the *CDKN2A*, *KIT* and *PTEN/PI3K/MTOR* pathways.

DNA methylation is a biological process by which methyl groups are added to the DNA molecule. Methylation can change the activity of a DNA segment without changing the sequence. When located in a gene promoter, DNA methylation typically acts to repress gene transcription.[52,53] Consequently, DNA methylation has a role in carcinogenesis. Bi et al. investigated the DNA methylation status of A and B thymomas.[52] Fifty-five common genes were found between the methylation and expression data of type A and B thymomas. Among them, 36 genes showed an inverse correlation between DNA methylation and expression alterations, in which seven genes were hypermethylated with low expression (*ICAM3*, *APBB1IP*, *IFI16*, *PARVG*, *CCM2*, *INPP5D*, *SP110*) and 29 were hypomethylated with high expression (*GALC*, *ALS2CR4*, *IQCC*, *RPL22*, *FEZ2*, *EPS15*, *KIF25*, *PACSIN2*, *PRKAR1A*, *PTPRE*, *ATP2A2*, *PNPLA8*, *SERPINB5*, *SGK3*, *CBLB*, *KLF11*, *C5orf45*, *SLC2A10*, *AUH*, *CPE*, *FBXO8*, *EEF1E1*, *STARD13*, *RAPGEF4*, *FSTL1*, *ZNF396*, *FRAS1*, *NAV2 and LCA5*).[52]

Tang et al. investigated the involvement of two metabolism-related genes (MRGs), *ASNS* and *BLVRA* in TET.[54] Both genes were strongly associated with survival in these patients. Hou et al. revealed that thymic carcinomas had significantly lower expression of *HMGB1*, a proinflammatory cytokine-related gene, compared to thymomas. Moreover, low *HMGB1* expression has been linked to a poor prognosis. Higher mutation rates were significantly associated with advanced stage and more advanced pathological types.[55] Li et al. investigated DNA methylation biomarkers where they showed that *cg05784862(KSR1)*, *cg07154254(ELF3)*, *cg02543462(ILRN)*, and *cg06288355(RAG1)* were independent prognostic factors for OS in patients with TET.[56]

Chromosome 6 is considered to harbor genetic abnormalities that lead to the development of thymomas.[57] Inoue et al. studied 40 thymomas. Genetic aberrations on chromosome 6 were found in 31 of 40 cases (77.5%) in five hot spots. The most frequent deletions on chromosome 6 were flanked by markers D6S441-D6S290 (6q25.2), D6S442-D6S1708 (6q25.2–25.3), D6S1666-D6S1560 (6p21.31), D6S1596-D6S284 (6q14.1–14.3), and D6S447-D6S1592 (6q21).[57]

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein with intrinsic tyrosine kinase activity.[58–61] Activation results in a variety of cellular responses including cell proliferation and differentiation. It has been shown that EGFR is expressed in thymic epithelial tumors and more particularly in advanced tumors.[58–61] Mutations have been identified in exons 18, 19, 20 and 21.[58] Although EGFR protein overexpression can be frequent (up to 69%), it does not correlate with gene amplifications.[59] In the study by Ionescu et al., of the 23 specimens with protein overexpression, only seven (30%) showed *EGFR* gene amplification by FISH.[59] Similarly, in the study by Suzuki et al., no *EGFR* gene mutations were detected in the 99 samples of thymomas and thymic carcinomas examined.[60] Consequently, there is a debate over the potential therapeutic value of anti-EGFR treatment of TET and further research in this field is warranted.[61]

Her2/Neu immunohistochemical protein overexpression is rare in thymomas but relatively frequent in thymic carcinomas.[62] However, no *HER2* gene amplification could be demonstrated by FISH in any tumor examined by Pan et al. Consequently, the authors conclude that an anti-HER-2/neu treatment is not an option in that particular context.

Bcl-2 is a proto-oncogene inhibiting apoptosis. *Bcl-2* is expressed most in medullary lymphocytes and epithelial cells of the normal thymus whereas *p53* is not expressed. *Bcl-2* and *p53* are coexpressed in the majority of the thymomas with increasing intensity in advanced stages.[63,64] It is thus considered that *Bcl-2* expression is a marker of aggressiveness in TET.

Most cancer cells present a telomerase activity that permits endless replication. One study showed that thymomas have a higher telomerase activity than thymic carcinomas but this is not correlated to tumor stage.[65] On the contrary, in thymic carcinoma, telomerase activity positively correlated with tumor stage.

Tumor angiogenesis is a critical step in tumor invasiveness. The expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in TET has been previously investigated.[66] In fact, there is a significant correlation between tumor angiogenesis and invasiveness in thymic epithelial tumors. On the other hand, thymic carcinomas have more aggressive angiogenic function than thymomas. A correlation between VEGF expression and invasive growth pattern in TET has been reported; however, it seems that angiogenesis depends less on the expression of bFGF.[65] Based on these findings, there have been several studies which have evaluated the efficacy of antiangiogenic agents against TETs, especially in cases of advanced and recurrent tumors with promising results.[67–69] Nevertheless, their administration is presently not the standard of care.

The degradation of extracellular matrix is another critical step that promotes tumor invasiveness and metastasis. This process is mainly conducted by proteolytic enzymes. Several studies have focused on the action of metalloproteinases (MMP) and their role in the invasiveness of TET.[69–71] More specifically, the gelatinolytic activity of active MMP-2 has been found to correlate with the invasiveness of thymic epithelial tumors.[69] In another study, MMP-2 and MMP-7 were predominantly expressed in type B3 and type C thymomas, respectively. MMP-9 was prominent in type B2 thymomas. Expression of MMP-2 or MMP-7 in tumor cells was also found to be correlated with clinical stage.[70] Sogawa et al. report that the higher the clinical stage of tumor, the stronger the MMP-2 positivity and tissue inhibitor of metalloproteinase-2 (TIMP-2) expression. Additionally, the expression of these molecules was predictive of poor prognosis compared to tumors with no expression.[72]

CONCLUSIONS

The carcinogenesis of TET is mostly unknown. The heterogeneity and rarity of these tumors render research difficulties. Despite the discrepancies among retrospective studies, there are some prognostic factors that are more pertinent such as the excision status and the Masaoka-Koga classification. The meticulous use of national and international databases could provide sufficient number of patients in order to draw safer conclusions. With the introduction of the new TNM classification system, patient registration should become easier and more homogeneous, providing higher numbers of patients that can be included in studies. On the other hand, the identification of different genetic pathways in the pathogenesis of TET represents a fascinating field of study that could possibly lead to the development of new targeted therapies. The promising results of studies investigating the efficacy of antiangiogenic agents, EGFR targeting and possibly immunotherapy should encourage further studies leading to new treatment options.

CONFLICT OF INTEREST

The authors have neither conflict of interest nor source of funding to declare.

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