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Report from the European Society of Thoracic Surgeons prospective thymic database 2017: A powerful resource for a collaborative global effort to manage thymic tumours

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(Article begins on next page)

1 **Report from the European Society of Thoracic Surgeons (ESTS) Database 2017. Preliminary**

2 **R**esults of the ESTS prospective thymic database: a powerful resource for the
3 collaborative global effort in the management of thymic tumors.

4
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34

35 **VISUAL ABSTRACT**

36

37 **KEY QUESTION:** The ESTS prospective thymic database was queried for analysis and for
38 comparison with the ESTS retrospective thymic database.

39

40 **KEY FINDINGS:** An increased use of minimally-invasive techniques and a wider use of
41 perioperative chemotherapy was observed.

42

43 **TAKE-HOME MESSAGE:** The ESTS prospective thymic database is a powerful tool open to any

44 ESTS Institution for the global effort in the management of thymic tumors.

45 **ABSTRACT**

46

47 *OBJECTIVES:* We queried the European Society of Thoracic Surgeons (ESTS) prospective thymic
48 database for descriptive analysis and for comparison with the ESTS retrospective thymic database
49 (1990-2010). *METHODS:* Data were retrieved (1/2007-11/2017) about 1122 patients from 75
50 ESTS Institutions. *RESULTS:* There were 484(65%) thymomas, 207(28%) thymic carcinoma and
51 49(7%) neuroendocrine thymic tumors (NETT). Staging (Masaoka) included 483(67%) Stage I and
52 II, 100(14%) Stage III, and 70(10%) Stage IV tumors. The new IASLC/ITMIG TNM classification
53 was available in 224 patients, including 177(85%) Stage I-II, 37(16%) Stage IIIA, 10(4%) Stage
54 IIIB. Chemotherapy as induction and adjuvant treatment was used in 14% and 15% of the patients.
55 Radiotherapy was almost exclusively employed postoperatively (24%). A minimally-invasive
56 surgical approach (VATS/RATS) was used in 276(33%) patients. Overall recurrence rate was
57 10.8%(N=38). As compared to the ESTS retrospective database, an increased prevalence of
58 thymic carcinomas (from 9% to 28%) and NETT (from 2% to 7%), an increased use of minimally-
59 invasive techniques (from 6% to 34%), and a wider use of chemotherapy as induction (from 9% to
60 15%) and adjuvant (from 2% to 16%) treatment was observed in the prospective database. The
61 introduction of a set of variables considered essential for the data use ("minimum dataset")
62 resulted in an increased average completeness rate. *CONCLUSIONS:* The reported data from the
63 ESTS prospective thymic database confirm the recent trends in the management of thymic tumors.
64 The ESTS prospective thymic database represents a powerful resource open to all ESTS
65 members for the global effort in the management of these rare tumors.

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67

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69 Abstract word count: 250

70

71 Keywords: Database, Thymus neoplasms, ESTS

72

73 **INTRODUCTION**

74

75 The European Society of Thoracic Surgeons (ESTS) is the largest pure thoracic surgery
76 society worldwide and its aim is to gather the experience of thoracic surgeons from different
77 continents in the different fields of thoracic surgery. Among the major initiatives of the Society,
78 there is the ESTS Registry, established in 2001 to collect the procedures for lung cancer among
79 ESTS members. After an initial limited number of procedures from few participating centres, the
80 project has gained an increasing and steady push forward and the number of procedures and
81 contributors have increased over the recent years. The 2017 registry report included more than
82 110,000 lung cancer patients from 240 participating units, and 145 institutions contributed with
83 more than 100 procedures.

84 The ESTS registry was recently implemented by adding some satellite databases collating data of
85 patients with other thoracic malignancies.

86 Among the ESTS satellite databases, the thymic registry was established in 2013 with the intent to
87 reunite the experience of as many ESTS institutions as possible with an interest in thymic tumors.

88 The thymic registry was the natural implementation of the initial ESTS retrospective thymic
89 database, established in 2010, that was managed by the ESTS thymic working group and which
90 collated data from 1990 to 2010. The unprecedented collection of data from the retrospective
91 database represented a major contribution to the development of the 8th TNM staging system of
92 thymic tumors (1), together with thymic databases from the International Thymic Malignancies
93 Interest Group (ITMIG) and the Japanese Association for Research on the Thymus (JART) and
94 under the coordination of the International Association for the Study of Lung Cancer (IASLC). After
95 the success of the retrospective database, it was decided to launch the prospective thymic
96 database project as satellite database of the ESTS Registry platform with the intent to provide an
97 up-to-date, online platform collecting claims and EMR (electronic medical record) data of patients
98 with thymic malignancies from ESTS institutions. The prospective ESTS thymic registry is under
99 the direct supervision of the ESTS Database Committee, and it is managed, audited and
100 periodically maintained by KData Clinical, the official platform of the ESTS Registry.

101 In the present paper the preliminary results of the ESTS prospective thymic registry are presented,
102 compared and discussed with the current available literature on thymic neoplasms and with the
103 ESTS thymic retrospective database to highlight the trends in the presentation and management of
104 thymic tumors in the ESTS community over the last decades.

105 **MATERIALS AND METHODS**

106

107 We downloaded from the ESTS registry satellite thymic database all the cases from the
108 prospective dataset. The collection of data started in 2010 and data from 2007 were retrieved until
109 November 2017. The retrieved data (forming the “ESTS_Data Base_Thymus” for the present
110 study) underwent a process of data cleaning before the analysis. The rate of completeness and
111 reliability rates of the core variables (2) were evaluated. The completeness and reliability
112 measurements were obtained following a standardized methodology (3). All the variables of
113 interest were collected and analysed, and the completeness of the data for each variable for a
114 preset number of variables considered “essential” was recorded. These variables constituted the
115 “minimum dataset”, which was defined as the minimum set of variables considered essential for
116 the use of the patient record. The list of the variables of the minimum dataset is shown in **Table 1**.
117 [The minimum dataset as well as information about cTNM and pTNM including N descriptor](#)
118 [according to the ITMIG/IASLC nodal map were introduced and implemented into the ESTS thymic](#)
119 [Registry in 2016.](#)

120

121

122 **RESULTS**

123

124 From January 2007 to November 2017 a total of 1122 patients were registered in the ESTS thymic
125 prospective database. The accrual rate increased steadily through the years, with an annual
126 accrual of more than 160 cases in the last 3 years. A total of 75 Institutions contributed to the
127 database, including 62 from Europe, 5 from Asia (4 from Turkey and 1 from Thailand), 7 from
128 South America (Brazil) and 1 from Africa (Morocco) ([Appendix 4 Supplemental file 1](#)). The
129 distribution of the European centres by country is shown in **Table 2**. The mean number of
130 patients/Institution was 15 (range 5-83).

131 **Table 3** summarizes the patient characteristics of the patient population.

132

133 *Demographics and preoperative characteristics.*

134 Mean age at diagnosis was 54 years; 414 patients (37%) were older than 50 at diagnosis. There
135 was an equal distribution between genders (50,2% male, 49.8% female). One third of the patients
136 (N=216, 32%) had Myasthenia Gravis at diagnosis. History of previous malignancy was recorded
137 in 82 cases (15%), mostly breast (N=13) and colon (N=10) cancer. A preoperative cyto/histologic
138 diagnosis was ~~deemed unnecessary~~ performed in 79.21% of the cases (N=434/115).

139

140 *Histology and staging.*

141 The majority of patients had thymoma (N=484, 65%); 207 (28%) had thymic carcinoma and 49
142 (7%) had neuroendocrine thymic tumors (NETT). In the thymoma group, 58% (N=253) had low-risk
143 tumors (A, AB, B1) while 183 (42%) had high-risk tumors (B2-B3). More than half of the patients
144 (N=399) presented with large tumors (> 5 cm). The most frequently involved structures at surgery
145 where the perithymic fat/mediastinal pleura (N=199, 30%), pericardium (N=50, 8%), lung (N=53,
146 8%), and brachiocephalic vessels/superior vena cava (N=59, 9%). The clinical (pretreatment) and
147 pathologic (post-surgical) Masaoka stage was recorded. At surgery, 34% (N=248) of the patients
148 were at Stage I, 33% (N=235) at Stage II, 14% (N=100) at Stage III, and 10% (N=70) at Stage IV.
149 In 24% of the cases, a clinical Stage I was not confirmed pathologically. Clinical Stage II was rarely

150 recorded (N=93, 17%), while pathological Stage II (Stage IIa/IIb) was much more frequently
151 reported (N=234, 33%). There was a good concordance between clinical and pathological Stage III
152 (N=77-14,1% vs. N=100-14.0%), Stage IVA (N=37-6.8% vs. N=45-6.3%) and Stage IVB (N=13-
153 2.4% vs. N=25-3.5%).

154 Information about the IASLC/ITMIG TNM classification (8th edition) was available in 224 patients,
155 both clinically and pathologically. More discordance was observed between cTNM and pTNM as
156 compared to cMasaoka and pMasaoka (Table 3): percentages in cTNM and pTNM for the different
157 T categories were as follows: T1: 70% and 56%; T2: 15% and 22%; T3: 10% and 16%; T4: 4%
158 and 4.4%. As for the N determinant, a very low frequency of N+ disease was reported (3%, N=7).
159 The frequency of M disease was 7% (N=17).

160

161 *Surgical information*

162 A complete resection was achieved in 89% of the cases (N=710). The most frequent extent of
163 resection included a complete thymectomy + thymomectomy (thymothymomectomy) in 90% of the
164 cases (N=682), while in 56 cases (7%) only thymomectomy was performed, leaving the thymus
165 behind. Of these there were 32 Stage I-II patients, which represents 6.6% of the entire Stage I-II
166 population (N=483). The most frequent reported surgical approach was ~~full-length total~~ sternotomy
167 (N=389), which was performed in almost half of the patients (48%). Minimally-invasive techniques
168 were employed in 33% (N=276) of the patients, including VATS (N=167, 20%) and Robotic
169 (N=109, 13%). Extended approaches (sterno-thoracotomy, hemi or clamshell) were reported in 5%
170 of the patients (N=41). The most frequently resected structures included the pericardium (N=110,
171 18%), the mediastinal pleura (N=93, 15%), the phrenic nerve (N=48, 8%). Resection of the great
172 venous vessels was not infrequent (brachiocephalic veins – 24 cases, superior vena cava – 9
173 cases). As for the associated lung resection for pulmonary involvement (N=112), the most frequent
174 procedure was a wedge resection, which was performed in 98 cases. Anatomic resections were
175 performed in 14 cases (segmentectomy, 1 case, lobectomy in 9 cases and pneumonectomy in 4
176 cases). Very rarely were other mediastinal/thoracic structures resected. Pleural procedures for

177 pleural involvement included resection of pleural implants (N=14), diaphragm (N=8) and
178 extrapleural pneumonectomy (EPP, N=3).

179

180 *Perioperative treatments and outcome.*

181 As for perioperative treatments, radiotherapy and chemotherapy were used as an adjunct to
182 surgery in different settings. Radiotherapy was used more often in an adjuvant (postoperative)
183 setting in 164 patients (25%), while chemotherapy was evenly employed in the preoperative setting
184 as an induction treatment (N=69) and in the postoperative (adjuvant) setting (N=71) in 15% and
185 16% of the patients, respectively.

186 The vast majority of patients were discharged alive from the hospital (N=939, 99%). ~~Only 5~~Five
187 patients died in hospital, and an additional 4 patients died at 30 days.

188 Overall, we had information about recurrence status in 451 patients. Of these, 49 patients
189 experienced a recurrence (10.8% recurrence rate). Eleven patients presented more than one
190 recurrence episode.

191

192 *Data completeness.*

193 **Figure 1** shows the completeness rate of the fields of the minimum dataset, which include the
194 datafields which are considered essential for the use of the record for the analysis. The median
195 completeness rate was 63.3%, ranging from 39.8% (chemotherapy) to 90% (WHO histology).

196

197

198

199

200 **DISCUSSION**

201

202 The present manuscript presents the preliminary results of the ESTS prospective thymic database
203 as of November 2017. It provides an overview of the clinical presentation, histology, staging and
204 management of thymic tumors among 75 ESTS Institutions.

205

206 *Clinical presentation and preoperative assessment.*

207 In the present registry thymic tumors occurred with almost equal frequency in males and females,
208 and in one-third of the cases they were associated with Myasthenia Gravis. This is in line with the
209 current literature (4, 5, 6).

210 An increased rate of extrathymic neoplasms in patients with thymic tumors was reported by Filosso
211 and associates (7). In our database, the overall rate of extrathymic tumors was 15%, of whom
212 breast and colon were the most frequent primaries.

213 The need of a preoperative cyto-histologic diagnosis was long required in the past. With the
214 advancements of radiologic imaging (last generation CT and MRI), a preoperative cyto-histologic
215 diagnosis of a suspected thymic tumors progressively lost its importance and is currently limited to
216 the infrequent occurrence of an equivocal radiologic imaging or in the presence of a non resectable
217 tumor to institute an induction treatment. This tendency had already been confirmed in a survey
218 among the ESTS members and in the retrospective ESTS database (8) and it is further evident in
219 the present report where 79% of the patients did not have a preoperative cyto/histologic
220 confirmation.

221

222 *WHO histology and staging*

223 The prevalence of the three different types of thymic tumors (thymoma, thymic carcinoma and
224 neuroendocrine thymic tumors, NETT) in the present database was 65%, 28% and 7%
225 respectively. The prevalences of thymic carcinoma and NETT are higher than the figures
226 commonly reported in the literature. Most of the largest series in the literature report a prevalence
227 of thymic carcinoma around 15-20% (9, 10, 11), with a far less prevalence for NETT (2-3%) (12,

228 **13**). We have no clear explanation for this prevalence difference in our database. The difference
229 might result from geographic distribution, dedicated referral or improved pathologic expertise in
230 differentiating B3 thymomas from thymic carcinoma. The tumor distribution is also different from
231 the one we observed in the ESTS retrospective database (1990-2010), where we reported a
232 prevalence of 88% for thymoma, 9% for thymic carcinoma, and 2% for the neuroendocrine thymic
233 tumors (**14, 15**).

234 In the present report information about the new IASLC/ITMIG TNM classification was available in
235 more than 200 patients. A good stage stratification was observed, although a wider discrepancy
236 between cTNM and pTNM was observed (particularly for early stages) as compared to clinical vs.
237 pathological Masaoka stage.

238

239 *Surgical approach and management*

240 A complete resection was performed in the vast majority of the patients (89%) and this reflects the
241 relatively high prevalence of Stage I-II disease (67%). The extent of thymectomy consisted in
242 resection of the thymic tumor only (thymomectomy) in 7.5% of the cases overall, and in 6.6% of
243 early stages (Stage I-II).

244 Controversy still exists in the literature whether in early stage (Stage I-II) non-myasthenic patients
245 thymomectomy alone (limited thymectomy) may be considered instead of the standard complete
246 thymectomy + thymomectomy. A recent paper from the JART database (**16**) found that 22.5%
247 (N=289/1286) patients with Stage I-II Masaoka stage actually received thymomectomy only,
248 leaving residual thymic tissue behind. A similar figure (24%, N=251/1047) was reported by Gu and
249 associates (**17**) enquiring the ChaRT database. An even higher rate of thymomectomies alone vs.
250 thymothymomectomy (39%, N=295/762) was reported by Narm and associates exploring the
251 KART database (**18**). The JART and ChaRT studies found no recurrence rate differences between
252 the two techniques. In the KART study, no recurrence rate difference was found in Stage I,
253 although a significantly higher recurrence rate was observed in patients with Stage II undergoing
254 limited thymectomy. The lower percentage of limited thymectomies (thymomectomy) in the ESTS
255 thymic database may reflect the traditional standard approach which has been used in Europe

256 over the last decades, with a general perception that limited thymectomy may predispose to
257 postoperative MG or a higher recurrence rate.

258

259 *Comparison of clinic-pathologic characteristics between the ESTS retrospective and prospective*
260 *databases.*

261 **Table 4** shows the clinico-pathologic characteristics of the patient population in the ESTS
262 retrospective and prospective thymic databases. The comparison may help clarify the trends over
263 time in the ESTS community about presentation and management of thymic tumors spanning over
264 almost 30 years (1990 to 2017). Median age, gender distribution, association with Myasthenia
265 Gravis, stage distribution (Masaoka stage), tumor size at resection, and complete resection rate
266 remained similar in the two databases. On the other hand, a significantly different distribution in
267 the tumor types (thymoma, thymic carcinoma, NETT) was reported in the prospective dataset, with
268 an increased prevalence in thymic carcinomas and NETT. As for the surgical approach, a
269 significantly increased use of minimally invasive techniques (VATS and RATS) was reported (from
270 4% to 20% for VATS and from 2% to 13% for RATS) with a consequent decrease of open
271 accesses. This is in line with most recent series from the largest international databases (**19**)
272 demonstrating a steady increase in the use of minimally invasive technique for thymic tumors in
273 the last years. A recent paper investigating the JART database report that currently 30% of
274 thymectomies in Japan are performed by VATS (**20**). A 20% prevalence of VATS was reported in a
275 recent paper from the ChART database from 1994 to 2010, with an increase up to 40% in the last
276 three years (**21**). Finally, in the ITMIG database, out of 2514 patients undergoing thymectomy for
277 thymoma from 1997 to 2012, 461 (18%) received a minimally-invasive approach (VATS or RATS),
278 with more than 70% in the last 2 years (**22**). As for the use of perioperative treatments, we
279 observed a wider use of chemotherapy in the prospective database, both as induction and as
280 adjuvant therapy (from 9% to 15% and from 2% to 16% respectively). The progressive increase in
281 the use of induction chemotherapy over the last years is in support of the conclusions of some
282 recent large series (**23**) and meta-analysis (**24**) and it reflects the wider compliance from the
283 contributing institutions to the current guidelines (**25**). Radiotherapy was similarly used in both

284 database, although with a slight reduction in the prospective data (25% vs. 29% in the
285 retrospective database). This indicates a general perception among the ESTS members of a
286 positive effect of postoperative radiotherapy after resection of thymic tumors which has not
287 changed over the last decades and which seems to be confirmed by two recent meta-analysis (26,
288 27).

289
290 *The international involvement of the ESTS prospective thymic registry.*

291
292 The ESTS thymic working group and the ESTS database committee have been actively involved in
293 the international big effort on thymic tumors which took place in the first decade of this millennium.
294 The leading thymic organization worldwide is the International Thymic Malignancies Interest Group
295 (ITMIG) which was founded in 2010 with the aim to promote and facilitate the integration among
296 disciplines, societies and organizations with an interest in thymic tumors and to provide
297 infrastructures and platforms to advance the clinical and basic research in these rare malignancies.
298 A number of thymic organizations are also active worldwide working in collaboration with ITMIG:
299 among these there are the Japanese Association for Research on the Thymus (JART), the
300 Chinese Alliance on Research in Thymomas (ChART), the Korean Association for research on the
301 Thymus (KART), and the Réseau Tumeurs THYMIques et Cancer (RYTHMIC). The ESTS thymic
302 working group was established in 2010 as a permanent working group of the Society. In the same
303 year the group launched the thymic retrospective database calling for the participation of any
304 interested ESTS Institution. The structure of the retrospective database was designed in
305 conjunction with ITMIG in order to have as many common datafields as possible to facilitate future
306 common studies. The response to the retrospective thymic database was enthusiastic and 35
307 centers joined the project. In few months the largest retrospective database of thymic tumors for
308 that time was collected. At the same time, IASLC called for the participation of international thymic
309 organizations for the second phase of the IASLC staging project for the 8th edition of the TNM
310 classification of thymic tumors. As a consequence of the call, a total of more than 10,000 cases
311 were collected, including 1814 from ESTS. The ESTS contribution to the 8th edition of the TNM

312 staging classification was recognized by IASLC. The ESTS thymic retrospective database provided
313 material for several studies, both alone (14, 15) and in association with ITMIG (10,11). In 2013
314 times were mature for the creation of the prospective thymic database. The ESTS Council and the
315 ESTS Database committees approved and funded the prospective thymic database project as a
316 satellite database of the ESTS Registry, using the official ESTS platform (Dendrite, later KData
317 Clinical). The great advantage of the prospective database is the more complete collection of data
318 and an overall increased data quality. The ESTS prospective database is online, user-friendly (see
319 [Appendix-Supplemental file 2](#) for instructions to access), free to all ESTS members, it is
320 periodically-maintained, it uses a standardized risk factors and outcomes, and it has the possibility
321 to export data for internal use from individual institutions, acting as institutional database. It also
322 represents a benchmark of performance and data quality for the individual surgeon and for the
323 Institution. The ESTS prospective database also represents a unique opportunity for any ESTS
324 contributor to propose studies using the data from the ESTS thymic registry. This is a great
325 opportunity among the ESTS members to contribute to thymic research using one of the largest
326 thymic databases in the world. A study draft illustrating the scope of the project and the expected
327 results should be sent to the ESTS Database Committee. The draft will be discussed by the
328 Committee and, if accepted, the contributor will receive the data for the analysis. Our co-authorship
329 policy includes that one person from each center which substantially contributed to the ESTS
330 thymic registry will be included in any manuscript submitted using the ESTS thymic database
331 under a list which allows each contributor to be linked to PubMed.

332 The structure of the ESTS thymic prospective database was designed from the retrospective
333 database while adding new datafields about imaging, pathology and the new TNM staging system.
334 Also, a big effort was undertaken in conjunction with ITMIG to harmonize the two databases,
335 similarly to what was done for the retrospective database, for common projects. The result was the
336 creation of a set of variables considered essential for the use of the record which are identical in
337 format and wording between the two databases.

338 A major issue in all databases, and particularly in multi-institutional databases, is the completeness
339 rate of the datafields, which in most clinical databases ranges from 20% to 85% depending on the

340 variables. The inputting of the data in the online prospective databases is very often a stepwise
341 process in different periods of time, usually done by trainees or junior doctors. This results in the
342 presence of many missing values which decrease the quality of the database. The 2015 ESTS
343 Database Annual report of the thymic prospective registry indicated a mean completeness rate of
344 40% (range 29%-90%) which was considered suboptimal. To address the issue we introduced the
345 concept of the "minimum dataset" which includes a set of variables which are considered essential
346 in order to use the record. The contributors are informed that their data cannot be used for studies
347 in case of incomplete information of the minimum dataset. Another tool to increase the
348 completeness rate was the institution of the Clinical Care Analysis (CCA) dashboard, which gives
349 the contributor a visual representation (in a dashboard) of his/her own data and their
350 completeness. Finally, periodical timely reminders to the contributors (twice a year) were also
351 considered of help to keep the momentum among the contributors. These implementations (the
352 minimum dataset, the CCA dashboard and the biannual reminders) were proposed to the
353 contributors and were introduced in 2016; as a consequence, the thymic report presented in the
354 2017 ESTS Database Annual Report resulted in a significant increase of the median completeness
355 rate (65%, range 42%-95%) as compared to the previous year (median 51%, range 27%-92%).
356 This positive trend was also evident at the last evaluation for the present analysis as of November
357 2017 (**Figure 1**)

358 The ESTS prospective thymic database is presently one of the three prospective thymic databases
359 in the world, along with ITMIG and RYTHMIC.

360 IASLC has recently launched the third phase of the IASLC staging Project for the 9th edition of the
361 TNM classification of thoracic malignancies, including thymic tumors (**28**). Once again, ESTS was
362 asked to provide the data from the prospective thymic database to be analysed, along with those
363 from the largest thymic organizations worldwide (ITMIG, JART, KART, RHYTMIC). The results of
364 this big collaborative global effort will provide a solid background for the next revision of the TNM
365 staging system of thymic tumors, expected in 2024.

366 Finally it is worth mentioning that, similarly to what has been done for the Core ESTS Dataset for
367 lung cancer, a possible further collaboration with Eepithor is under discussion and it is likely to be
368 finalized in the near future.

369

370 *Strenghts and limitations.*

371 Some limitations are associated with the present report. First, although prospective, the data
372 collection remains heterogeneous and reflects different individual expertises, including a lack of a
373 centralized pathologic review, and a non-uniform attitude towards perioperative treatments. Also,
374 the relatively few cases with a detailed TNM classification makes it difficult to provide sound
375 evidence about the applicability and the effectiveness of the new staging classification. Finally,
376 although a significant increase in the completeness rate was observed during the last years, some
377 datafields still include a considerable numbers of missing information, which may limit the use of
378 these records for analysis.

379 On the other hand, the present report presents the results of one of the currently largest
380 prospective thymic databases in the world. The potential impact of the information and the
381 continuous data upload provided by the use of the official ESTS platform guarantee a good data
382 reliability.

383

384 In conclusion, the preliminary results of the ESTS thymic prospective database confirm the general
385 changes in presentation, diagnosis and management of thymic tumors which have been reported
386 in the current literature, including a trend towards a widespread use of minimally-invasive resection
387 techniques, and an increase adoption of chemotherapy both in the induction and in the adjuvant
388 setting. The information of the present database may represent a valuable source of data which
389 can be used for collaborative studies with other major thymic organizations and for the 9th revision
390 of the TNM classification of thymic tumors.

391

392 **CONFLICT OF INTEREST:** None

393

394 **TABLES.**

395

396

397 **Table 1.**

398

399 ESTS Thymic Minimum dataset – Minimum standard datafields to be completed for data analysis

400

- 401 • Gender (Male/Female)
- 402 • Date of Birth
- 403 • Date of surgery
- 404 • Paraneoplastic associated syndromes (MG*, etc)
- 405 • Final pathologic diagnosis (thymoma, thymic carcinoma, NETT**)
- 406 • WHO histology
- 407 • Thymic carcinoma histology
- 408 • Neuroendocrine Thymic Tumor (NETT) histology
- 409 • Pathologic Masaoka Stage
- 410 • Final pathologic resection status (R0, R1, R2§)
- 411 • Pathologic TNM stage (IASLC/ITMIG staging, 8th Ed. TNM)
- 412 • Outcome at discharge (Alive/dead)
- 413 • Chemotherapy (Intent, Date initiated)
- 414 • Radiotherapy (Intent, Date initiated)
- 415 • Date of death or last follow-up date
- 416 • Vital status

417

418 *Myasthenia Gravis

419 **Neuroendocrine Thymic Tumors

420 § R0: Complete resection; R1: Incomplete resection (microscopic); R2: Incomplete resection
421 (macroscopic)

422

423

424
425
426
427
428
429

Table 2.

Distribution of European contributors to the ESTS thymic prospective database by country.

Country	No. of centers
Italy	14
Spain	11
Hungary	9
Belgium	5
Portugal	4
Greece	3
Romania	3
Austria	2
Germany	2
The Netherlands	2
Croatia	1
Switzerland	1
United Kingdom	1

430
431

432
433
434
435
436

Table 3.

Patients characteristics of the ESTS thymic prospective database.

	Number	%*
Gender		
<i>Male</i>	563	50.2
<i>Female</i>	559	49.8
Age (Mean, range)	54 (5-91)	
Associated paraneoplastic syndromes		
<i>None</i>	431	63.8
<i>Myasthenia Gravis</i>	216	32.0
<i>Hypogammaglobulinemia</i>	6	0.9
<i>Red cell aplasia</i>	1	0.1
<i>Other autoimmune</i>	24	3.6
Previous malignancy		
<i>None</i>	475	86
<i>Breast</i>	13	2.4
<i>Lung</i>	6	1.1
<i>Colon</i>	10	1.8
<i>Prostate</i>	9	1.6
<i>Skin</i>	3	0.5
<i>Lymphoma</i>	3	0.5
<i>Other</i>	38	7
Preoperative diagnosis required		
<i>No</i>	434	79
<i>Yes</i>	116	21
Histology		
<i>Thymoma</i>	484	65
• <i>A</i>	58	13.3
• <i>AB</i>	116	26.6
• <i>B1</i>	79	18.1
• <i>B2</i>	112	25.7
• <i>B3</i>	71	16.3
<i>Thymic carcinoma</i>	207	28
<i>Neuroendocrine thymic tumor (NETT)</i>	49	6.6
Tumor size		
<i>< 3cm</i>	116	16.3
<i>3-5 cm.</i>	196	27.6
<i>>5 cm.</i>	399	56.1
Clinical Masaoka Stage		
<i>I</i>	328	60
<i>Ila</i>	51	9.3
<i>Ilb</i>	42	7.7
<i>III</i>	77	14.1

<i>IVa</i>	37	6.8
<i>IVb</i>	13	2.4
Pathologic Masaoka Stage		
<i>I</i>	248	34.7
<i>IIa</i>	134	18.8
<i>IIb</i>	101	14.1
<i>III</i>	100	14.0
<i>IVa</i>	45	6.3
<i>IVb</i>	25	3.5
Clinical TNM		
<i>T1</i>	140	70.0
<i>T2</i>	31	15.5
<i>T3</i>	21	10.5
<i>T4</i>	8	4
<i>N0</i>	205	95.7
<i>N1</i>	8	3.7
<i>N2</i>	1	0.5
<i>M0</i>	193	92.7
<i>M1</i>	15	7.3
Pathological TNM		
<i>T1</i>	126	56.2
<i>T2</i>	51	22.7
<i>T3</i>	37	16.5
<i>T4</i>	10	4.4
<i>N0</i>	213	96.8
<i>N1</i>	3	1.3
<i>N2</i>	4	1.8
<i>M0</i>	205	92.3
<i>M1</i>	17	7.6
Completeness of resection		
<i>Complete (R0)</i>	710	89.0
<i>Microscopic residual (R1)</i>	61	7.6
<i>Macroscopic residual (R2)</i>	20	2.5
Chemotherapy		
<i>No</i>	309	69.1
<i>Induction</i>	61	13.6
<i>Adjuvant</i>	63	14.1
<i>Palliative</i>	6	1.3
<i>Both pre/post</i>	8	1.8
Radiotherapy		
<i>No</i>	472	72.6
<i>Induction</i>	11	1.7
<i>Adjuvant</i>	158	24.3
<i>Palliative</i>	3	0.5
<i>Both pre/post</i>	6	0.9
Surgical approach		
<i>Sternotomy</i>	389	47.7
<i>Thoracotomy</i>	93	11.4
<i>Clamshell/Hemiclamshell</i>	26	3.2
<i>VATS</i>	167	20.5
<i>Robotic (RATS)</i>	109	13.4

<i>Transcervical</i>	7	0.9
<i>Transcervical + sternal split</i>	10	1.2
<i>Sterno-thoracotomy</i>	15	1.8
Extent of thymectomy		
<i>Thymomectomy only</i>	682	92.4
<i>Thymothymomectomy</i>	56	7.5
Recurrence		
One episode	38	10.8
More than one episode	11	

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Table 4.

Comparison between the prospective vs. the retrospective ESTS thymic database.

	Retrospective database	Prospective database
Years of collection	1990-2010	2007-2017
No. of patients	2151	1122
No. of Institutions	35 (27 from Europe)	75 (62 from Europe)
Age (median)	56	54
Males/Females (No./%)	1042/1109 (51%/49%)	563/559 (50%/50%)
Myasthenia Gravis	629 (35%)	216 (32%)
T size (median)	6	5.5
Stage (Masaoka)		
I	672 (34%)	248 (38%)
II	699 (35%)	235 (36%)
III	410 (20%)	100 (15%)
IV	215 (11%)	70 (11%)
WHO Histology		
Thymoma low-grade (A-AB-B1)	1018 (50%)	253 (58%)
Thymoma high-grade (B2-B3)	780 (38%)	183 (42%)
Thymic carcinoma	191 (9%)	207 (28%)
NETT	41 (2%)	49 (7%)
Surgical approach	N=1956	N=816
Open	1824 (93%)	540 (66%)
Simple°	1716 (88%)	499 (61%)
Extended°	96 (5%)	41 (5%)
VATS	88 (4%)	167 (20%)
RATS	44 (2%)	109 (13%)
Complete resection (R0)	1709 (88%)	710 (89%)
Mean No. of pts treated by center (Yearly)		
<4 (19 centers, 54%)	532 (26%)	
5-9 (11 centers, 31%)	680 (33%)	
>10 (5 centers, 14%)	818 (40%)	
Induction therapy	239 (13%)	86 (17%)
CT alone	170 (9%)	69 (15%)
RT alone	12 (1%)	17 (3%)
CT + RT	57 (3%)	NA
Adjuvant therapy	853 (44%)	235 (43%)
CT alone	54 (2%)	71 (16%)
RT alone	566 (29%)	164 (25%)
CT + RT	243 (12%)	NA

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Figure legends.

Figure 1.

Completeness rate for the datafields of the minimum dataset. Comparison between 2016 and ~~November~~ 2017.

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462 **Appendix 4**

463 **Contributing Institutions to the ESTS prospective thymic database-**

- 464 [Central Chest Institute of Thailand, Thailand \(A. Omehai\)](#)
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472 [Hopital Academique Erasme, Belgium \(M. Cappello\)](#)
473 [University Hospitals Leuven, Belgium \(D. Van Raemdonck\)](#)
474 [ZOL St. Jan Genk, Belgium \(G. Lauwers\)](#)
475 [St Augustinus, Antwerp, Belgium \(Deleersnijder\)](#)
476 [Hospital Júlia Kubitscheck \(L. Rodrigues\)](#)
477 [Sainte Marguerite University Hospital, Aix Marseille University, Marseille, France \(P. Thomas\)](#)
478 [AHEPA University Hospital, Thessaloniki, Greece \(C. Foroulis\)](#)
479 [Evangelismos Hospital, Athens, Greece \(C. Zisis\)](#)
480 [Theagenio Hospital, Greece \(Barbotakis\)](#)
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487 [Pamok Győr Hungars, Hungary \(T. Molnar\)](#)
488 [Bács-Kiskun County Teaching Hospital, Hungary \(Kovacs\)](#)
489 [Semmelweis Teaching Hospital – Miskolc Hungary \(Toth\)](#)
490 [Markusevsky University Hospital, Hungary \(Laszlo\)](#)
491 [Koranyi National Institute for Pulmonology and Semmelweis University, Hungary \(Vagvolgyi\)](#)
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496 [Ospedali Riuniti, Università di Foggia, Italy \(F. Sollitto\)](#)
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501 [AOU Careggi, SOD Chirurgia Toracica, Firenze \(L. Voltolini\)](#)
502 [AOU S. Maria Della Misericordia, Italy \(F. Londero\)](#)
503 [National Cancer Institute, Pascale Foundation, Naples, Italy \(G. Rocco\)](#)
504 [European Institute of Oncology, Milan, Italy \(L. Spaggiari\)](#)
505 [VUMC Department of Surgery, The Netherlands \(J. Oosterhuis\)](#)
506 [Amphia Hospital, The Netherlands \(E. Veen\)](#)
507 [Santa Martha Hospital, Lisbon, Portugal \(I. Gomes Bravio\)](#)
508 [Centro Hospitalar de Vila Nova de Gaia Espinho – Portugal \(J. Miranda\)](#)
509 [Luz Hospital, Lisbon, Portugal \(P. Martelo\)](#)
510 [Marius Nasta Institute of Pneumonology, Romania \(C. Bolca\)](#)
511 [Clinical Municipal Emergency Hospital, Romania \(A. Nicodin\)](#)
512 [Institute of Oncology Bucharest, Romania \(C. Motas\)](#)
513 [University Hospital of Salamanca, Spain \(N. Nevea\)](#)

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515 [H. Clinico San Carlos, Spain \(Hernando\)](#)
516 [Sagrat Cor University Hospital, Barcelona, Spain \(J. Fibla\)](#)
517 [HHUU Virgen del Rocío, Madrid, Spain \(P. Moreno\)](#)
518 [General University Hospital, Valencia, Spain \(Figueroa\)](#)
519 [Hospital Clinic, Barcelona University, Spain \(L. Molins\)](#)
520 [University Virgen Macarena Hospital, Spain \(M. Congregado\)](#)
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523 [Ramon y Cajal University Hospital, Madrid, Spain \(Nico\)](#)
524 [Kantonspital St. Gallen, Sweden \(Dutly\)](#)
525 [University College London Hospital, UK \(M. Scarsi\)](#)
526 [Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Brazil \(R. Terra\)](#)
527 [Hospital São Lucas da PUCRS, Brazil \(M. Tsukazan\)](#)
528 [Pavilhão Pereira Filho—Santa Casa de Porto Alegre, Brazil \(S. Camargo\)](#)
529 [Hospital de Base do Distrito Federal—Asa Sul, Brasília, Brazil \(Humberto\)](#)
530 [Hospital Santa Isabel—Nazaré, Salvador, Brazil \(G. Fortunato\)](#)
531 [Hospital Brasília, Lago Sul, Brasília, Brazil \(N. Ferreira de Lima\)](#)
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Appendix 2.

Instructions for access to the online ESTS thymic prospective database.

Eligibility criteria: ESTS active member (ESTS membership status is checked before providing database credentials)

1. Log in at <http://www.ests.org>
2. Click on "Collaboration" → European Database.
3. Click on "Database Registration Form" → Registration Form.
4. Download the Registration form.
5. Complete the form with the required information and send it to the addresses provided (KData Clinical Administrators)
6. You will receive the credentials for your Institutions for logging into the Database.
7. Direct access to the ESTS Registry: log in at <https://ests.kdataclinical.it>

Once logged into the Database:

8. Click on "Search/Add" → "Add new patient"
9. You need to complete the fields with the demographics data.
10. Then you will see a menu with the thymic sections (Preop Thymus, Op Thymus, Postop Thymus, F.up Thymus).
11. Start completing the fields.
12. The mandatory fields (i.e. the minimum dataset fields) are highlighted.

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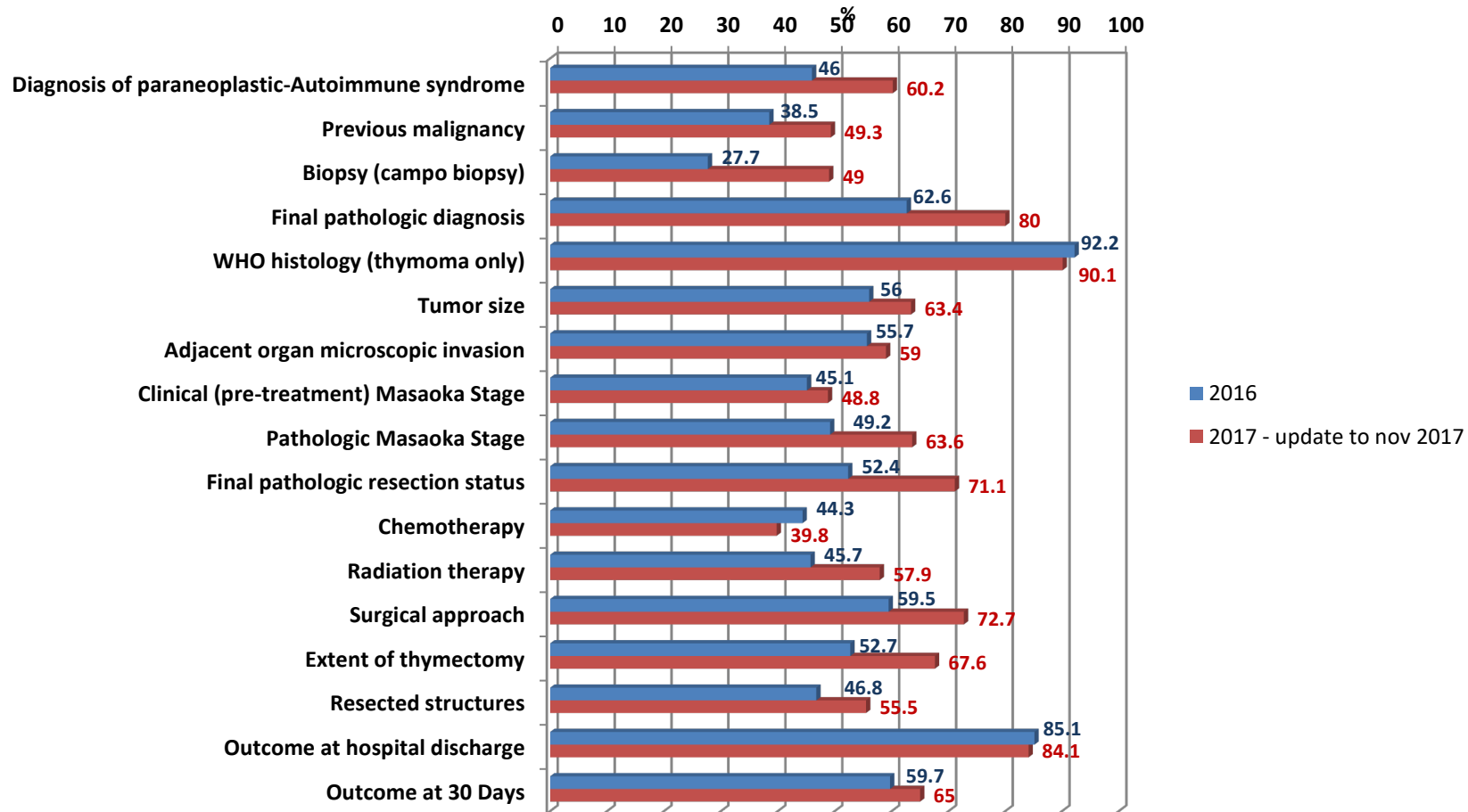
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Appendix 1

Contributing Institutions to the ESTS prospective thymic database.

Central Chest Institute of Thailand, Thailand (A. Omchai)
Istanbul University Medical School, Istanbul, Turkey (A. Toker)
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Medical University of Vienna, Vienna, Austria (B. Moser)
University Hospital of Antwerp, Antwerp, Belgium (P. Van Schil)
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University Hospitals Leuven, Belgium (D. Van Raemdonck)
ZOL St.-Jan Genk, Belgium (G. Lauwers)
St Augustinus, Antwerp, Belgium (Deleersnijder)
Hospital Júlia Kubitscheck (L. Rodrigues)
Sainte Marguerite University Hospital, Aix-Marseille University, Marseille, France (P. Thomas)
AHEPA University Hospital, Thessaloniki, Greece (C. Foroulis)
Evangelismos Hospital, Athens, Greece (C. Zisis)
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Bács-Kiskun County Teaching Hospital, Hungary (Kovacs)
Szemmelweis Teaching Hospital - Miskolc Hungary (Toth)
Markusovszky University Hospital, Hungary (Laszlo)
Koranyi National Institute for Pulmonology and Semmelweis University, Hungary (Vagvolgyi)
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Appendix 2.

Instructions for access to the online ESTS thymic prospective database.

Eligibility criteria: ESTS active member (ESTS membership status is checked before providing database credentials)

1. Log in at <http://www.ests.org>
2. Click on "Collaboration" - > European Database.
3. Click on "Database Registration Form" -> Registration Form.
4. Download the Registration form.
5. Complete the form with the required information and send it to the addresses provided (KData Clinical Administrators)
6. You will receive the credentials for your Institutions for logging into the Database.

7. Direct access to the ESTS Registry: log in at <https://ests.kdataclinical.it>

Once logged into the Database:

8. Click on "Search/Add" -> "Add new patient"
9. You need to complete the fields with the demographics data.
10. Then you will see a menu with the thymic sections (Preop Thymus, Op Thymus, Postop Thymus, F.up Thymus).
11. Start completing the fields.
12. The mandatory fields (i.e. the minimum dataset fields) are highlighted.