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**Title: Characteristics of Patients with Large-Cell Neuroendocrine Carcinoma of the Lung**

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**Abstract**

**Aim:** Lung's Neuroendocrine tumors are a clearly different group of tumors that have definite ultrastructural, immunohistochemical, and molecular features. We reported and analyzed the incidence, clinicopathologic features, rates of surgery, responses to first-line therapy, and survival outcomes of this rare tumor of the lung according to our lung cancer patient database.

**Methods:** 62 patients with Large Cell Neuroendocrine Carcinoma of Lung (LCNEC) who were diagnosed histopathologically between January 2010 and January 2016 recorded retrospectively.

**Results:** The patients' average age was 60.3±8.6. Male predominated %95 (male/female= 59/3). Diagnosis was made by the fine-needle aspiration biopsy (NAB) in 7 patients, bronchoscopic transbronchial biopsy (TBB) in 13 patients and surgery in 42 patients. Most commonly tumor was localized in the right upper lobe (43.5%). Also, 46.8% of all patients were in peripheral location. Sixteen patients were stage 1, 17 patients were stage 2, 15 patients were stage 3 and 14 patients

were stage 4. Median progression-free survival (PFS) was 29 months (SE:12.2) (95% CI, 5.2–52.8 months). Progression-free survival (PFS) was significantly better in patients who have low N, M0, early stage, p63 positive and TTF-1 positive across the whole cohort. Overall survival (OS) was significantly better in patients who have low N, M0, low stage, peripheral location across the whole cohort.

**Conclusion:** Our study demonstrates a single center experience with clinicopathologic factors and survival outcomes of LCNEC patients, which is a rare group of thoracic malignancies.

K**ey words:** large-cell neuroendocrine carcinoma of the lung, progression-free survival, overall survival, stage, TTF-1

**Introduction**

Lung's Neuroendocrine tumors are a clearly different group of tumors that have definite ultrastructural, immunohistochemical, and molecular features [1]. Pulmonary neuroendocrine tumors include four tumor subtypes. These are; low grade typical carcinoid tumor, intermediate grade atypical carcinoid tumor, high grade large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma [2]. These constitute approximately 25% of all primary pulmonary carcinomas. The most of them are formed from SCLC. LCNEC is rare and its incidence varies between 2.1 and 3.5% [3-4]. LCNEC were first-time described by Travis et al in 1991 as tumors formed of large cell morphology with a low nuclear-to-cytoplasmic ratio, a high mitotic activity (>10 mitoses per 10 high-power fields(HPF)), dense necrosis, in addition neuroendocrine differentiation (by immunohistochemistry or electron microscopy) [5]. These features were accepted by World Health Organization (WHO) as diagnostic criteria, in 1999.

While the previously World Health Organization (WHO-2004) classification categorized LCNEC as a variant of large cell carcinomas in the lung neuroendocrine tumor group, currently WHO-2015 classification, LCNEC is classified as a group of neuroendocrine neoplasms with SCLC, TCT, and ACT [2,6]. While LCNEC has a worse prognosis compared with both NSCLC and large cell carcinomas without neuroendocrine differentiation, it is similar to the poor prognosis of SCLC. LCNEC's are recommended to be treated like SCLC [7-8]. But LCNEC are substantially less chemo-responsive to platinum/etoposide regimen [9]. Also, the prognosis of LCNEC is heterogeneous and there is no proven treatment. For this reason, we wanted to evaluate the clinico-pathologic features, diagnosis and treatment of our patients with large cell neuroendocrine carcinoma of the lung, for contributing

to the literature.

## Materials and Methods

### Patients

62 patients with Large-Cell Neuroendocrine Carcinoma of the Lung who were diagnosed histopathologically in Hospital between January 2010 and January 2016 recorded retrospectively. Patients' age, gender, laboratory parameters, diagnostic pattern, tumor characteristics, staging, tumor localization, treatment including surgery, radiation and systemic therapy, chemotherapy regimen, immunohistochemistry features and mortality were recorded.

Seventh version of International Association for the Study of Lung Cancer (IASLC) (TNM) was used for staging tumor, node, metastasis [10]. The follow-up evaluations consisted of physical examination, serum biochemistry, complete blood cell counts, CT scans of thorax, and other imaging examinations if indicated. The intervals of clinical and imaging examinations were performed every three months for the first year. For the following 2 years examinations were performed for every 6 months and annually thereafter. Based on the radiologic or histologic examination disease progression was determined. The overall survival was calculated (OS) starting from the beginning of treatment to the time of death or last follow-up. Progression-free survival (PFS) was defined as the time from the beginning of treatment to the time of tumor progression or last follow-up. Formal retrospective Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 assessment was performed for all patients with available diagnostic imaging for radiological response evaluation [11] . ORR could not calculated in patients with available radiologic imaging, suitable for assessment by RECIST 1.1.

### Pathology

Pathological diagnosis of LCNEC was established according to the 2015 WHO classification. Diagnostic criteria were large cell size, necrosis, low nuclear/cytoplasm ratio, presence of neuroendocrine morphology (palisading, organoid nesting, trabeculae, and/or rosettes), high mitotic rate, defined as > 10 mitoses per 10 high-power fields (HPF) and immunohistochemical expression of at least one neuroendocrine marker such as chromogranin-A, synaptophysin, CD56/NCAM (neural cell adhesion molecule) [6]. The Ki-67 labeling index was the indicator of high-grade malignancy.



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The presence of non-small-cell cytomorphological features (abundant cytoplasm, prominent nucleoli and/or vesicular chromatin) was used in the differential diagnosis of LCNEC and SCLC. We also excluded squamous cell carcinomas by positive thyroid transcription factor-1 (TTF-1), p63, and cytokeratin 5/6. We excluded adenocarcinomas by positive periodic acid-schiff and alcian blue staining.

**Statistical analysis**

All analyses were conducted by SPSS 17.0 (SPSS, Chicago, IL, U.S.A.) statistical software. Categorical variables were described by frequencies and percentages, numerical variables were presented by means and standard deviations or by medians and minimum-maximum values. Kaplan Meier Analyses were conducted to calculate median survival times of compared factors. Multivariate COX regression analysis was applied to calculate HR values. A p-value of less than 0.05 was chosen to state statistically significant difference between investigated parameters.

**Ethics**

The study was conducted according to good clinical practice and the Declaration of Helsinki. The study was approved by the ethics committee of the hospital (No: 49109414-806.02.02). Because of the studies retrospective design written consent form would not be able to obtain from the participants.

**Results**

Sixtytwo of the 13088 patients diagnosed with lung cancer were Large-Cell Neuroendocrine Carcinoma between January 2010 and January 2016. The patients' average age was 60.3±8.6. Male predominated %95 (male/female= 59/3). Diagnosis was made by the fine-needle aspiration biopsy (NAB) in 7 patients, bronchoscopic transbronchial biopsy (TBB) in 13 patients and surgery in 42 patients. The tumor was localized most commonly in the right upper lobe (43.5%). Also, 46.8% of all patients were in peripheral location. Tumor stage, location and localization are summarized in table-1. Sixteen patients were stage 1, 17 patients were stage 2, 15 patients were stage 3 and 14 patients were stage 4. Fourteen patients (22.6%) had distant metastasis at the time of diagnosis, metastatic



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sites were as follows: liver (8 patients), bone (6 patients), brain (4 patients), adrenal gland (2 patients) and lung (2 patients). Forty-two patients at clinical TNM Stage I, II or IIIA were surgically resected, two patients were medical inoperable. Most patients underwent lobectomy (34 patients, 81%) and followed by pneumonectomy (7 patients, 16.7%), respectively. Thirty four patients (54.8%) received systemic chemotherapy (60% cisplatin etoposide, 15% carboplatin etoposide, 25% platinum-based combined chemotherapy including gemcitabine or vinorelbine). Nine of the operated patients were diagnosed as NSCLC by Transbronchial fine needle aspiration biopsy or Transthoracic fine needle aspiration biopsy before surgery so they operated accordingly. After operation pathological specimens showed that these patients were LCNEC. Progression was seen in 32 patients and half of them were treated after progression. 5 patients received second line chemotherapy, 8 patients received palliative radiotherapy and 3 patients received chemoradiotherapy.

CD56 in 55 patients, synaptophysin in 37 patients, chromogranin in 13 patients, p63 in 10 patients, CK5-6 in 4 patients, CK 7 in 41 patients, TTF-1 in 25 patients, NE in 5 patients, were positive, respectively. Progression-free survival was significantly worse in p63 and TTF-1 negative cases (respectively p 0.017 and 0.042) (Figure 1).

Median progression-free survival (PFS) was 29 months (SE:12.2) (95% CI, 5.2–52.8 months) (Table 2). Progression-free survival (PFS) was significantly better in patients who have low N, M0, low stage, p63 positive and TTF-1 positive across the whole cohort (Figure 2). But progression-free survival (PFS) was significantly worse in patients who have chemotherapy combined with palliative radiotherapy due to progression. Median overall survival (OS) was 20 months (SE:8.6) (95% CI, 3.1–36.9 months) (Table 3). Overall survival (OS) was significantly better in patients who have low N, M0, low stage, peripheral location across the whole cohort. But overall survival (OS) was significantly worse in patients who had progression requiring palliative radiotherapy.

**Discussion**

In this study, we report a large number of patients with LCNECs of the lung. We analyzed the incidence of this rare tumor of the lung according to our lung cancer patient database, and we informed stages, clinico-pathologic features, rates of surgery, responses to first-line therapy, and survival outcomes of this cohort.

LCNECs are primarily observed in male patients (M:F = 17:1) [12]. Our cohort was also male predominated %95 (male/female = 59/3), which was consistent with the known demographics in this disease. The diagnoses were mainly performed by surgery (42/62) in our cohort of patients. In the literature, most LCNECs have been diagnosed postoperatively by surgical specimens [13, 14]. In the literature LCNECs are often peripherally- or midzone-located [12]. In our study, the tumor was peripherally located in 46.8% of all patients.

The clinical and biological characteristics of LCNEC are similar to those of SCLC; however, LCNEC is currently classified as non-SCLC. Therefore, there is a dilemma concerning whether to use SCLC-based or non-SCLC-based regimens for patients with LCNEC. As part of the present study, we reported that most of our patients treated with a platinum-based regimen (SCLC-based), whereas the minority of patients was treated with non-SCLC-based regimens.

In the relevant literature, when treating LCNEC patients, the response rate to platinum-based chemotherapy was 60%, while the response rate to non-platinum-based chemotherapy remained 11% [15]. Moreover, the aforementioned study showed whether advanced LCNEC should be treated similarly to SCLC versus non-SCLC with respect to chemotherapeutic regimens. In this study, the authors concluded that advanced LCNEC could be treated appropriately in a manner similar to SCLC rather than NSCLC. As part of the present study, thirty-four patients (54.8%) received systemic chemotherapy (60% cisplatin-etoposide, 15% carboplatin etoposide, 25% platinum-based combined chemotherapy including gemcitabine or vinorelbine), especially for adjuvant setting. Only one patient received neoadjuvant chemotherapy. A certain progression was seen in 32 patients and half of them were treated after progression. Five patients received second-line chemotherapy. We were unfortunately unable to calculate the response rates because of the available radiological imaging.

Patients with LCNEC had poor prognoses. Five-year survival rates in pathological stage I cases is 27-67% and average five-year survival rates is 15-57% [16-18]. Iyoda et al. compared the 5-year



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survival rate of patients with pathological stage IA LCNEC with same stage patients with adenocarcinomas or squamous cell carcinomas of the lung and found that 54.5 versus 89.3 % respectively [19]. In the present study, the median PFS was 29 (95% CI, 5.2-52.8 months) and median overall survival was 20 (95% CI, 3.1-36.9 months). We aim to report the 5-year survival of this cohort in the near future.

In the literature relevant to patients with non-squamous non-small cell lung cancer, TTF-1 expression was independently associated with overall survival and progression-free survival. For LCNEC tumors, TTF-1 is used to exclude the diagnosis; however, in our study TTF-1 expression was correlated with a better PFS. There was no difference in terms of OS. This may be due to the heterogeneity of the tumor morphology. Also, in our study, PFS and OS were correlated with the stage of the tumor as expected.

Our results must be considered in the context of the limitations of the study. Firstly, this is a single-center retrospective database study. Therefore, the patients in this study come from a specific region and may not reflect the whole population. Because of the retrospective design of the study, it is possible that some clinical characteristics may not have been recorded. Moreover, due to the rarity of this tumor, the number of participants in the study was low for subgroup divisions, thus for some comparisons the number of patients in each group did not reached the level required for statistical significance.

**Conclusion**

Our study demonstrates clinic, pathologic factors and survival outcomes of LCNEC patients, which is a rare group of thoracic malignancies. We believe that it is important to conduct prospective randomized trials with numbers of patients as high as possible.



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**Table 1. Tumor stage, location and localization in patients with Large-Cell Neuroendocrine Carcinoma of the Lung**

| | |
|---|---|
| **Age (mean±SD)** | 60.3±8.6 |
| **Gender (n,%)** | |
| Male | 59 (%95.2) |
| Female | 3 (%4.8) |
| **Diagnostic pattern (n, %)** | |
| NAB | 7 (%11.2) |
| TBB | 13 (%21) |
| Surgery | 42 (%67.8) |
| **T (n, %)** | |
| T1 | 14 (%22.5) |
| T2 | 29 (%46.8) |
| T3 | 7 (%11.3) |
| T4 | 12 (%19.4) |
| **N (n, %)** | |
| N0 | 31 (%50) |

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| | |
|---|---|
| N1 | 9 (%14.6) |
| N2 | 11 (%17.7) |
| N3 | 11 (%17.7) |
| **Metastasis (n, %)** | |
| M0 | 48 (%77.4) |
| M1 | 14 (%22.6) |
| **Stage (n, %)** | |
| 1A | 8 (%13) |
| 1B | 8 (%13) |
| 2A | 11 (%17.7) |
| 2B | 6 (%9.6) |
| 3A | 11 (%17.7) |
| 3B | 4 (%6.5) |
| 4 | 14 (%22.5) |
| **Tumor localization** (n, %) | |
| right upper lobe | 27 (%43.5) |
| Left upper lobe | 15 (%24.2) |
| middle lobe | 4 (%6.5) |
| right lower lobe | 6 (%9.7) |
| left lower lobe | 10 (%16.1) |
| **location** (n, %) | |
| Peripheral | 29 (%46.8) |
| Central | 33 (%53.2) |
| **Chemotherapy (n,%)** | |
| - | 28 (%45.2) |
| + | 34 (%54.8) |
| **Chemotherapy regimen (n,%)** | |
| carboplatin etoposide | 5 (%15.2) |
| cisplatin etoposide | 20 (%60.6) |
| other regimens | 9 (%24.2) |



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| | |
|---|---|
| **Radiotherapy (n,%)** | |
| - | 42 (%68) |
| + | 20 (%32) |
| **Surgery (n,%)** | |
| Lobectomy | 34 (%81) |
| Pneumonectomy | 7 (%16.7) |
| Segmentectomy | 1 (%2.3) |
| **Progression (n,%%)** | |
| - | 26 (%44.8) |
| + | 32 (%55.2) |
| **post-progression therapy (n,%)** | |
| - | 16 (%50) |
| + | 16 (%50) |
| **Time to progression (month) (median,IQR)** | 14 (45.5) |
| **Duration of follow-up (month) (medyan,IQR)** | 21.5 (44) |
| **Status (n,%)** | |
| Living | 24(%39) |
| Ex | 38(%61) |

**Table 2. Progression-free survival**

| | Median (SE) | %95 CI | p |
|---|---|---|---|
| **Diagnostic pattern** | | | |
| NAB | 5 (6.1) | 0-17.0 | |
| TBB | 6 (1.6) | 2.9-9.1 | **<0.001** |
| Surgery | - | - | |
| **T** | | | |
| T1 | - | - | 0.195 |



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| | | | |
|---|---|---|---|
| T2 | 14 (11.2) | 0-36.0 | |
| T3 | 25 (23) | 0-70.1 | |
| T4 | 10 (16.2) | 0-41.8 | |
| **N** | | | |
| N0 | - | - | |
| N1 | 20 (7.9) | 4.6-35.4 | **<0.001** |
| N2 | 5 (1.5) | 2.1-7.9 | |
| N3 | 3 (2.4) | 0-7.6 | |
| **M** | | | |
| M0 | 53 (-) | - | **<0.001** |
| M1 | 3 (2.7) | 0-8.4 | |
| **Stage** | | | |
| I | - | - | |
| II | 39 (12.6) | 14.3-63.7 | **<0.001** |
| III | 8 (3.2) | 1.7-14.3 | |
| IV | 3 (2.7) | 0-8.4 | |
| **Location** | | | |
| Peripheral | 53(-) | - | 0.143 |
| Central | 14(10.7) | 0-34.9 | |
| **Chemotherapy** | | | |
| - | - | - | |
| + | 10 (4.9) | 0.3-19.7 | **0.046** |
| **Chemotherapy regimen** | | | |
| carboplatin etoposide | 6 (3.3) | 0-12.4 | 0.205 |
| cisplatin etoposide | 7 (1.1) | 4.8-9.2 | |
| other | - | - | |



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| | | | |
|---|---|---|---|
| **Radiotherapy** | | | |
| **-** | - | - | **<0.001** |
| + | 6 (1.3) | 3.4-8.6 | |
| **Surgery** | | | |
| Lobectomy | 53(-) | - | 0.242 |
| Pneumonectomy | - | - | |
| **P 63** | | | |
| **-** | 20(10.5) | 0-40.5 | **0.017** |
| + | - | - | |
| **TTF-1** | | | |
| **-** | 20 11.8) | 0-43.1 | **0.042** |
| + | - | - | |



**Table 3. Overall Survival**

| | Median (SE) | %95 CI | p |
|---|---|---|---|
| **Diagnostic pattern** | | | |
| NAB | 7 (3.7) | 0-14.2 | |
| TBB | 2 (2.4) | 0-6.7 | **<0.001** |
| Surgery | - | - | |
| **T** | | | |
| T1 | - | - | 0.280 |
| T2 | 20 (4.2) | 11.7-28.3 | |

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| | | | |
|---|---|---|---|
| T3 | 8 (12.2) | 0-32.0 | |
| T4 | 12 (6.9) | 0-25.6 | |
| **N** | | | |
| N0 | - | - | |
| N1 | 23 (4.5) | 14.2-31.8 | **<0.001** |
| N2 | 8 (1.6) | 4.9-11.1 | |
| N3 | 4 (1.5) | 0.9-7.0 | |
| **M** | | | |
| M0 | 59 (23.1) | 13.7-104 | **<0.001** |
| M1 | 4 (1.8) | 0.6-7.4 | |
| **Stage** | | | |
| I | - | - | |
| II | 46 (10.4) | 25.7-66.3 | **<0.001** |
| III | 12 (4.8) | 2.5-21.5 | |
| IV | 4 (1.6) | 0.6-7.4 | |
| **location** | | | |
| Peripheral | - | - | **0.042** |
| Central | 20 (4.7) | 10.8-29.2 | |
| **Chemotherapy** | | | |
| - | 27 (18.4) | 0-63 | 0.842 |
| + | 20 (3.6) | 12.9-27.1 | |
| **Chemotherapy regimen** | | | |
| carboplatin etoposide | 10 (5.5) | 0-20.7 | 0.557 |
| cisplatin etoposide | 18 (6) | 6.3-29.7 | |
| other | 59 (29.6) | 1.0-117 | |
| **Radiotherapy** | | | |
| - | 59 (-) | - | **0.001** |
| + | 10 (2.2) | 5.8-14.2 | |



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| | | | |
|---|---|---|---|
| **P 63** | | | |
| - | 20 (5.4) | 9.4-30.6 | 0.215 |
| + | - | - | |
| **TTF-1** | | | |
| - | 20 (9.6) | 1.3-38.7 | 0.219 |
| + | - | - | |
| **Progression (n,%%)** | | | |
| - | - | - | **<0.001** |
| + | 12 (5.6) | 0.9-23.1 | |
| **OS** | 20 (8.6) | 3.1-36.9 | |

**Figure 1. Correlation between cumulative survival and p63 positivity**

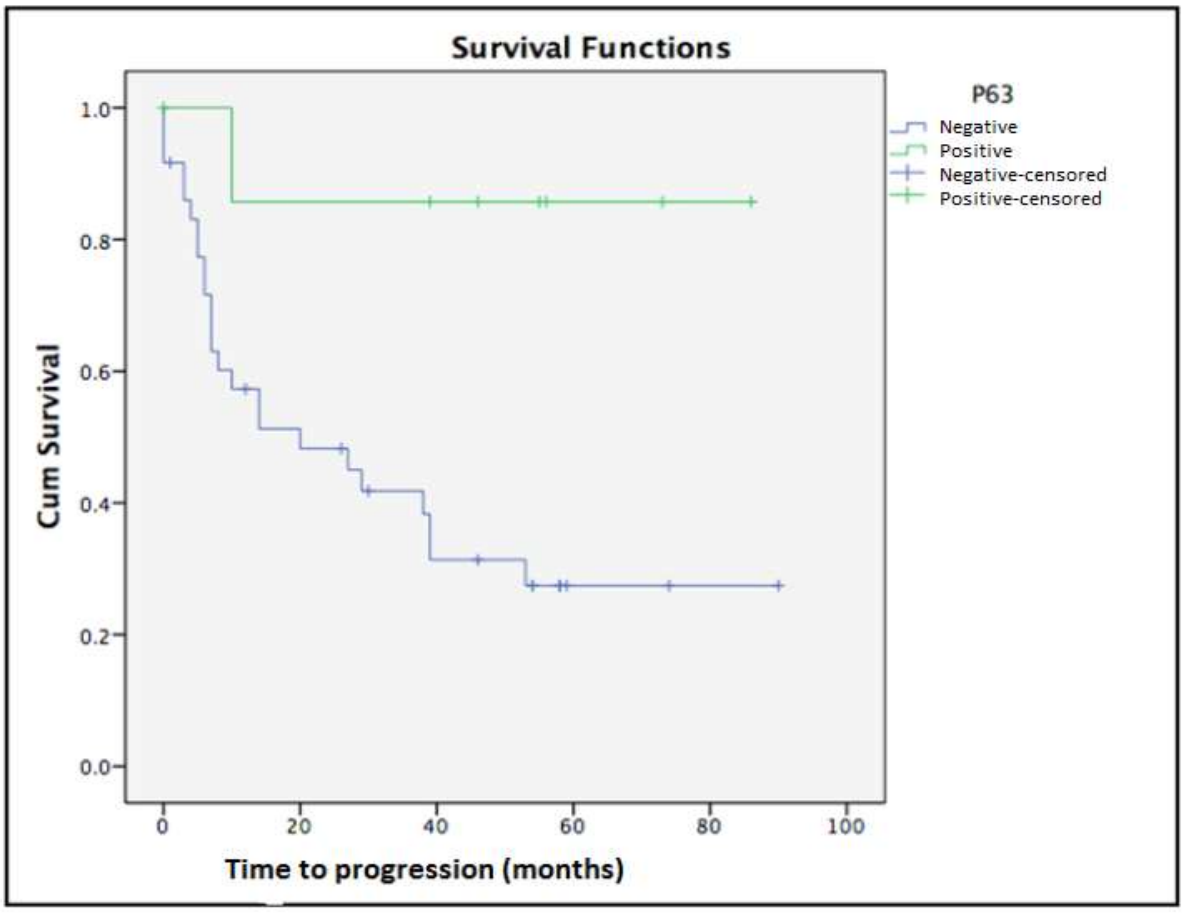

**Figure 2. Correlation between cumulative survival and TTF1 positivity**