Gitte Dam

OPFØLGNING HOS PATIENTER MED TYPISK LUNGE NET BEHANDLET MED KIRURGI

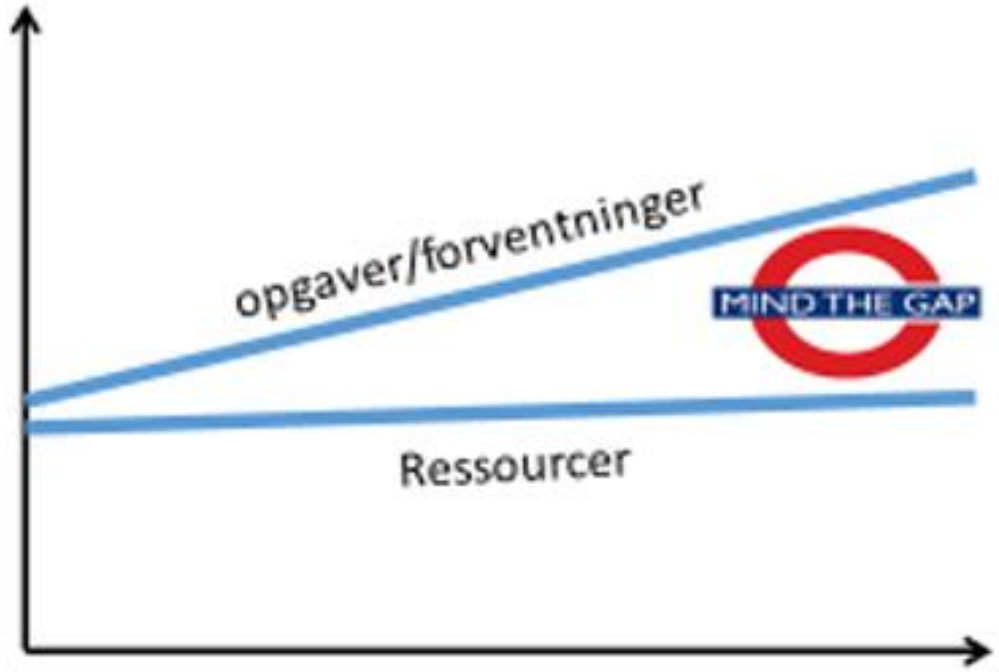
– ER KONTROL INDICERET?

* Tobias Stemann Lau, Patrick Soldath, Karina Stubkjær Rewitz, Peter Jepsen, Ulrich Knigge, Seppo Langer, René Horsleben Petersen, Mikkel Andreassen, Gitte Dam

AARHUS UNIVERSITET
INSTITUT FOR KLINISK MEDICIN

midt regionmidtjylland

Veldrevet hospital i transformation



Veldrevethed handler om at anvende de ressourcer, vi har, så de skaber mest mulig værdi for patienterne og sikrer en bæredygtig organisation. Effektiv ledelse og fælles styringsredskaber, klare mål, veldefinerede processer, et godt arbejdsmiljø og en stærk kvalitetskultur bidrager bl.a. til veldrevethed.

Vi kan ikke blive ved med at drive hospital på samme måde som vi gør nu. Så kommer vi til at mangle ressourcer og kapacitet. Derfor har vi brug for **transformation**:


NHS
TREATMENTS
One in, one out?

Vigtigt med ledelsesopbakning!

Aktuelt

Lægefaglige direktører: Vi vil støtte lægerne i at prioritere

Hospitalslægerne skal have frihed til at prioritere mellem patienter, så de, der trænger mest, behandles først. Det kan politikerne ikke, og det ansvar vil vi hjælpe lægerne med at løfte, skriver fem lægelige l

Ledelsesopbakningen gælder for alle faggrupper

PROCES OMKRING LUNGE NET

- Forundring/nysgerrighed
- Undersøgelse - forskningsprojekt
- Fremlæggelse kongres
- Artikel
- Guidelines ændres

Prognosis of Patients with **Bronchopulmonary** Neuroendocrine Neoplasms in a Tertiary Neuroendocrine Tumor Centre of Excellence.

Rewitz KS, Grønbæk H, Tabaksblat EM, Dahl Baunwall SM, **Dam G.**

Neuroendocrinology. 2022;112(12):1214-1224. doi: 10.1159/000525379. Epub 2022 Jun 7.

PMID: 35671706

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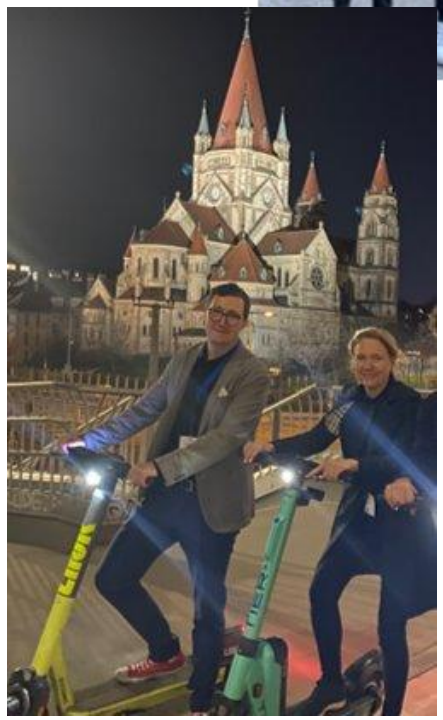
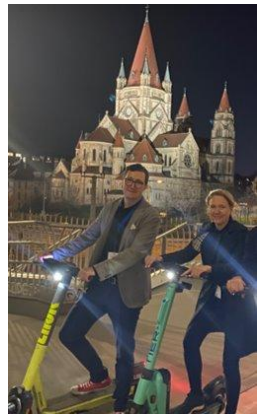
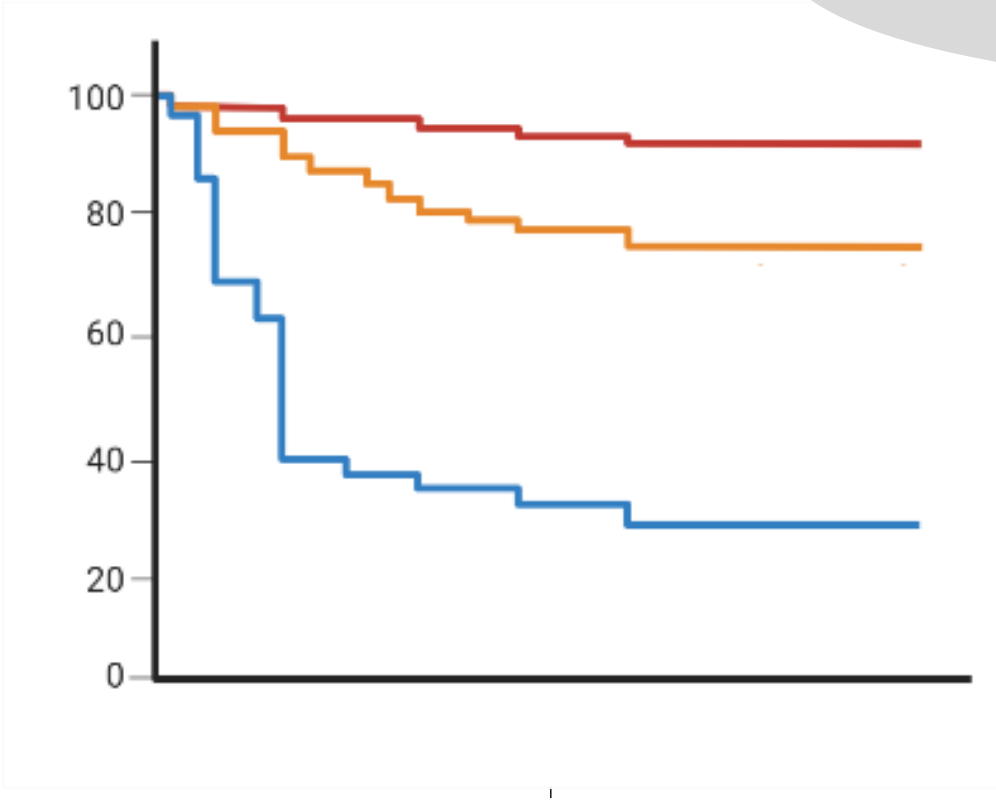


Er der undergrupper uden tilbgefald



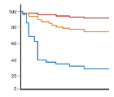
Væksthastighed ? Lymfeknuder? Tumorstørrelse



LUNGE NET

Terminology	Differentation	Mitotic count	Necrosis
Typical carcinoids (TC)	Well-differentiated	< 2	No
Atypical carcinoids (AC)	Well-differentiated	2-10	Yes/no

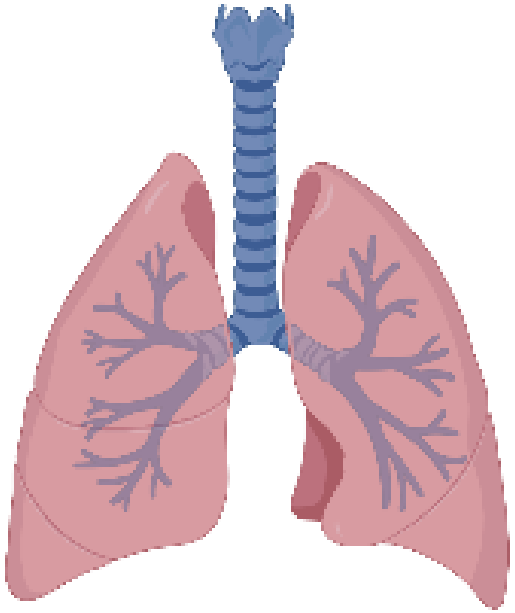
Kirurgisk resektion – oftest med kurativt sigte



Lav risiko for recidiv og god prognose

Langvarigt og ekstensivt follow-up program efter kurativ kirurgi

Ingen skelnen mellem TC og AC – på trods af at TC har bedre prognose



FOLLOW-UP PROGRAM

CT scanning af thorax og abdomen

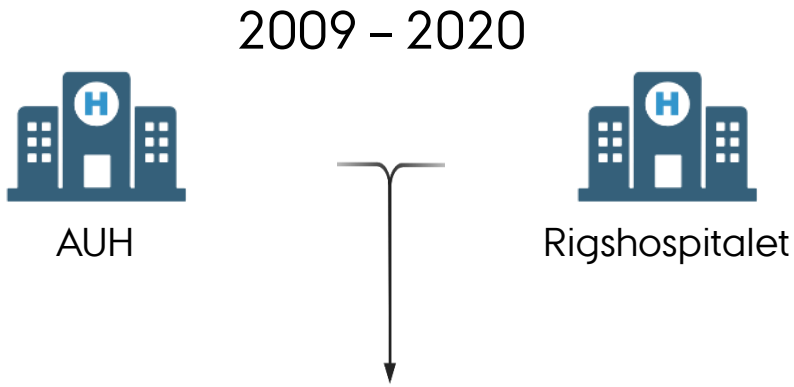
- 0-2 år: Halvårligt
- 2-5 år: Årligt
- 5-10 år: Hvert andet år
- Efter 10 år: Individuel vurdering

FORMÅL

- At se på risikoen for tilbagefald hos patienter med typisk lunge carcinoid (TC) efter kirurgi (kurativt sigte)

- At diskutere, hvorvidt det nuværende omfattende og langvarige kontrolforløb kan retfærdiggøres

DESIGN OG STATISTIK



Patienter med Typisk lunge NET behandlet med kurativt sigte, dvs.:

- Ingen metastaser
- Hele tumor fjernet (R0-resektion)

Fulgt fra operationsdato indtil enten:

- Recidiv
- Død (competing risk)
- Administrativ end of follow-up (maj 2024)

ALLE PATIENTER

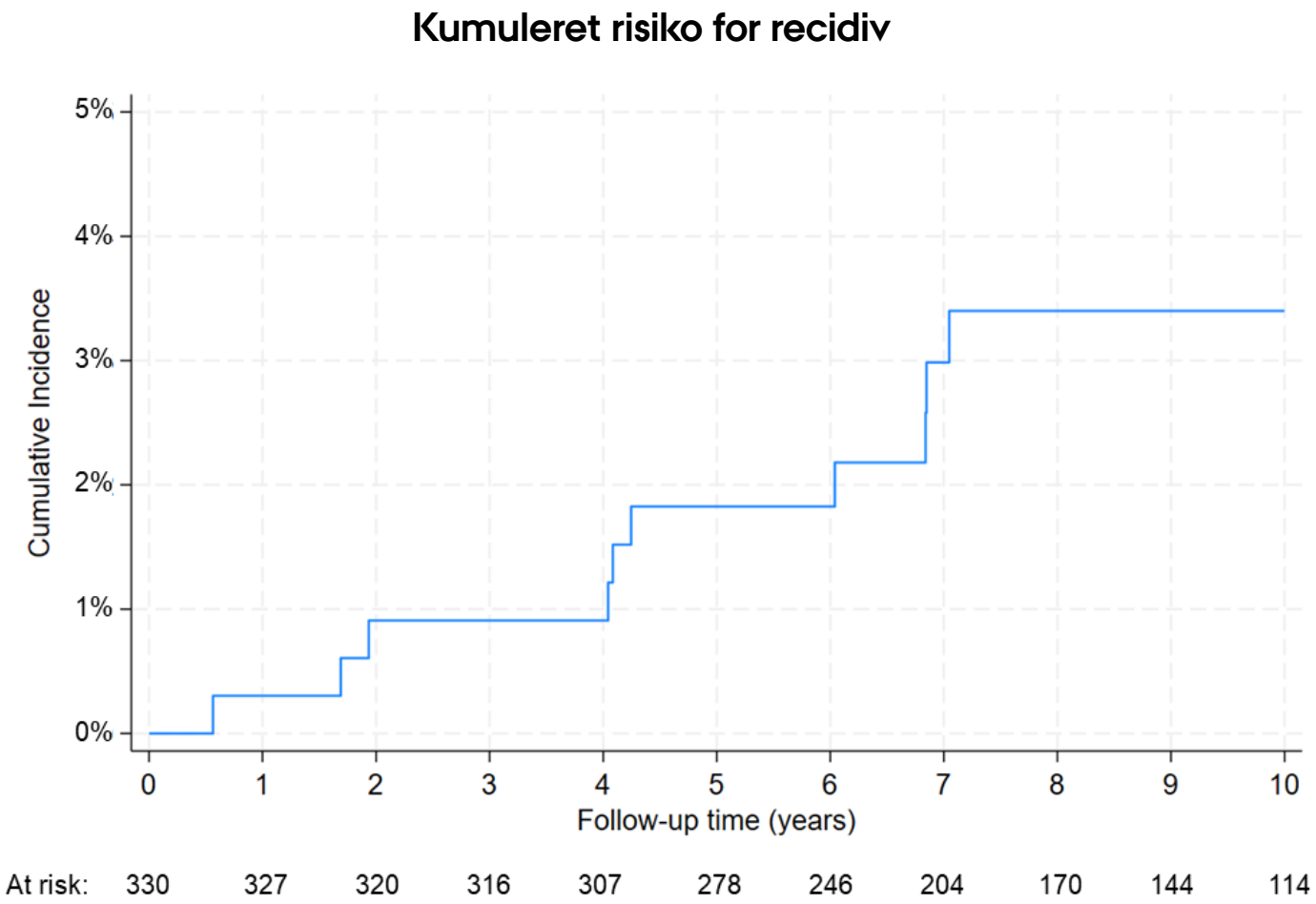
330 patienter

2.806 år
Median: 8,1 år (IQR: 5,9 – 11,2)

10 recidiver

10 års kumuleret risiko for recidiv:

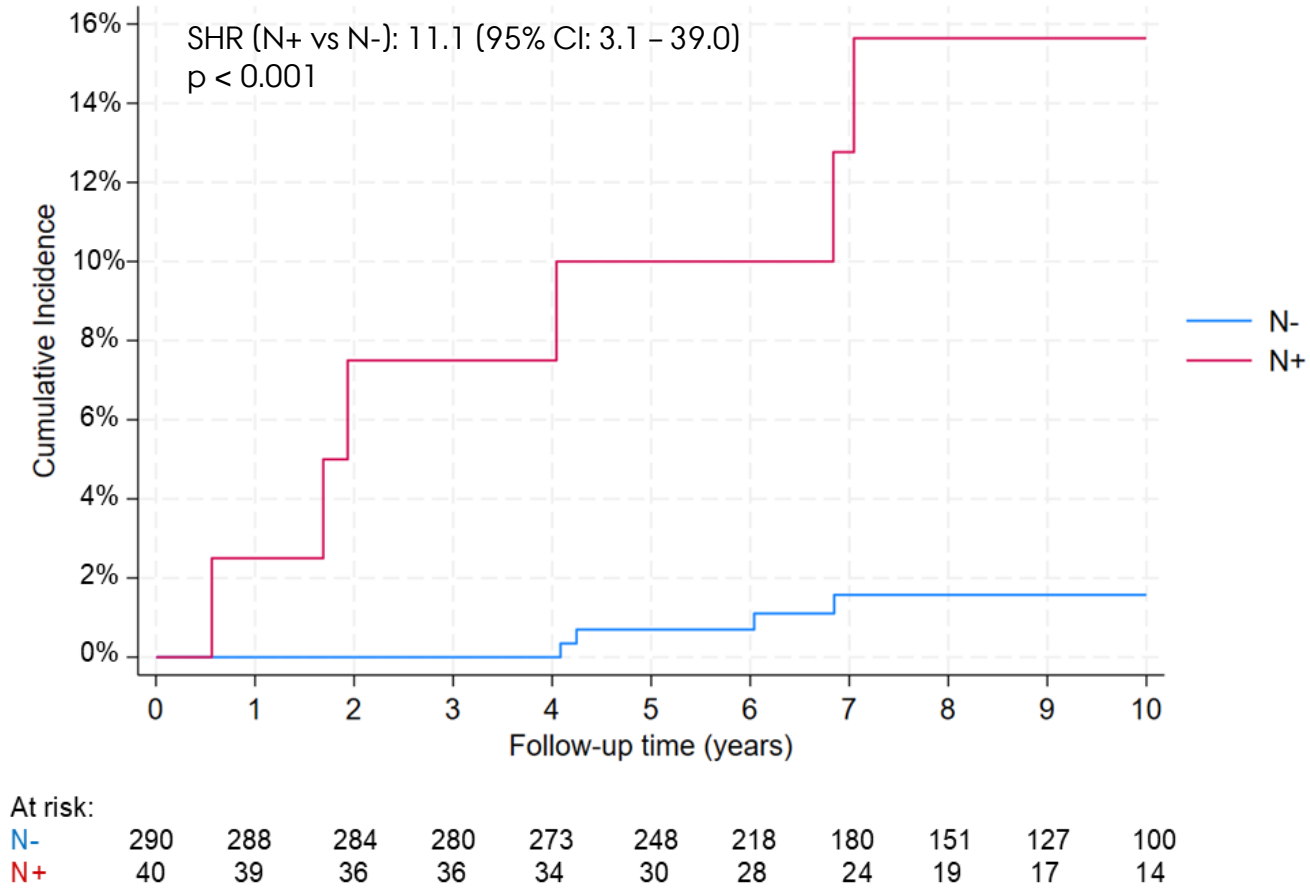
Alle patienter: 3,4 % (95% CI: 1,7 – 6,0)



N-STATUS

Table. Summary of baseline characteristics

	All (n=330)	No recurrence (n=320)	Recurrence (n=10)
T-classification			
T1 – T2	309 (94%)	300 (94%)	9 (90%)
T3 – T4	21 (6%)	20 (6%)	1 (10%)
N-classification			
N -	290 (88%)	286 (89%)	4 (40%)
N +	40 (12%)	34 (11%)	6 (60%)



10 års kumuleret risiko for recidiv:

N-	1,6 %	(95% CI: 0,5 – 3,8)
N+	15,6 %	(95% CI: 6,3 – 28,8)

Risiko for stråleinduceret cancer ved kontrolprogram[1]

- Kvinde, 18 år: 3,1 %
- Kvinde, 30 år: 1,4 %
- Tilbagefald 1,6% (1/4 blev behandlet igen)

[1] Heijboer et al., Lung Cancer, 2024

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

Follow-Up is Not Justified in Patients with Typical Lung Carcinoids Treated with Curative Intent

T.S. **Lau**[1,2,3], P. **Soldath**[4,5,6], K.S. **Rewitz**[1,2,3], P. **Jepsen**[1,2,3,7], U. **Knigge**[5,8,9], S.W **Langer**[5,6,10], R.H. **Petersen**[4,5,6], M. **Andreassen**[5,6,9], G. **Dam**[1,2,3]

[1]Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark [2]ENETS Center of Excellence, Aarhus University Hospital, Aarhus, Denmark [3]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark [4]Department of Cardiothoracic Surgery, Rigshospitalet, Copenhagen, Denmark [5]ENETS Center of Excellence, Rigshospitalet, Copenhagen, Denmark [6]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark [7]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark [8]Department of Gastrointestinal Surgery, Rigshospitalet, Copenhagen [9]Department of Nephrology and Endocrinology, Rigshospitalet, Copenhagen, Denmark [10]Department of Oncology, Rigshospitalet, Copenhagen

Poster ID: A17

Background

Typical Carcinoids (TC) are well-differentiated neuroendocrine neoplasm (NEN) of the lung.

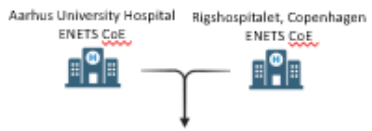
After treatment with curative intent, recurrences are rare, and TC are associated with a very favorable prognosis.

The prognostic significance of lymph-node status and tumor size on recurrence risk is unclear.

Current follow-up guidelines from ENETS and ESMO recommend comprehensive and long-term follow-up including regular computed tomography (CT) imaging with substantial radiation exposure.

Methods

Patients included



- From 2009 – 2020: All TC patients diagnosed at the two centers were assessed
- Inclusion criteria:
  - TC patients treated with surgical curative intent
  - No distant metastases (M0)

Statistics

- Aalen Johansen method to estimate the cumulative incidence of recurrence at 1, 3, 5, and 10 years, treating death as a competing risk
- Fine Gray subdistribution hazard ratios to evaluate the effect of lymph-node involvement (yes vs no) and tumor size (T1-T2 vs T3-T4)

Aim

Primary aim

To investigate the risk of recurrence in patients with TC treated with surgically curative intent, focusing on the prognostic significance of N- and T-status.

Secondary aim

To discuss the justification of the currently recommended comprehensive and long-term follow-up program in these patients.

CONCLUSION

- Patients with TC without lymph node involvement have very low risk of recurrence
- The benefits of the current follow-up program are outweighed by the substantial radiation exposure and derived risk of radiation-induced cancer as a result of the follow-up program
- We recommend tailoring the follow-up program based on lymph node status, with **node-negative patients being excluded from regular follow-up programs**

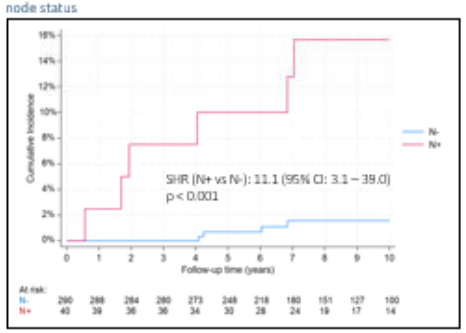
Results

- 330 patients included in the analysis
- Total follow-up time: 2,806 years, median 8.1 years (IQR: 5.9 – 11.2)
- Patients with recurrence: 10
  - 4 without lymph node involvement at diagnosis
  - 6 with lymph node involvement at diagnosis
- **10-year cumulative risk of recurrence for patients without lymph node involvement: 1.6 %**

Table 1. Baseline characteristics at time of surgery. *Missing data on 13 patients

	No recurrence (n=320)	Recurrence (n=10)
Age	63 (52-71)	65 (59-68)
Female sex	231 (72%)	4 (40%)
Tumor location**		
Central	145 (48 %)	5 (56 %)
Peripheral	156 (52 %)	4 (44 %)
T-classification		
T1-T2	300 (94%)	9 (90%)
T3-T4	20 (6%)	1 (10%)
N-classification		
N-	286 (89%)	4 (40%)
N+	34 (11%)	6 (60%)

Figure 1. Cumulative incidence (risk of recurrence) according to lymph node status



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Til Tobias Stemann Lau

Cc Tobias Stemann Lau; patrick.soldath@regionh.dk; Karina Stubkjær Rewitz; Peter Jepsen; Ulrich.Peter.Knigge@regionh.dk; seppo.langer@regionh.dk; rene.horsleben.petersen@regionh.dk; mikkel.andreassen.01@regionh.dk; Gitte Aarøe Dam

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with treatment, nothing is mentioned about diagnosis: how the diagnosis was made, imaging, histology confirmation prior to surgical intervention.
Collection of information: "All recurrence were reviewed by an experience clinician and/or pathologist." This sentence could be included in recurrence section.
Statistical First few lines could come to initial part of study design.

Results:
Follow up time: at many places authors have mentioned 2806 years, 2483 years, 323 years etc: need to correct it.
Last line for results: tumour size did not affect the risk ..... : this needs to be rephrased

Discussion part: Authors mention that TC patients with LN negative should be discharged after radical surgery: what are their views on post operative functional imaging and cross sectional imaging to confirm no local disease?
Authors should review a recent study: involving 10244 patients from UK and US database: https://doi.org/10.1530/ERC-25-0211 (Marie Line El Asmar et at, Endocrine related cancer ERC-25-0211)

Referee: 2

Comments to the Author
This Danish multicenter ENETS Centers of Excellence cohort study analyzed 330 patients with typical lung carcinoids (TC) treated with radical surgery between 2009 and 2020. Median follow-up was 8.1 years. Overall, the 10-year cumulative recurrence risk was 3.4%, but it was only 1.6% in node-negative patients versus 15.6% in those with lymph node involvement (SHR 11.1, p<0.001). Tumor size had no significant impact on recurrence. Most recurrences were detected by routine follow-up imaging, but in node-negative patients, only one of four recurrences led to curative-intent treatment. Given the low recurrence risk and potential harms from surveillance (radiation, false positives), the authors recommend omitting regular follow-up in node-negative TC patients, while continuing it for node-positive cases.
While the dataset is sizeable and the analytic framework employs appropriate competing-risks methods for the primary endpoint, there are several limitations to be discussed.
1. The study design is a retrospective historical cohort drawn from two ENETS Centers of Excellence, with inclusion restricted to histologically confirmed typical carcinoids resected with curative intent (R0, M0). Although such a restriction reduces heterogeneity, it also narrows external validity to high-volume expert settings. Surgical quality, perioperative staging, and multidisciplinary adjudication in ENETS centers may not reflect community practice, where understaging and variation in resection/systematic nodal dissection are more frequent; recommendations based on this experience may therefore not translate to broader healthcare environments. The authors themselves acknowledge the predominance of lobectomy, the relatively small tumors, and the expert context, all of which select for favorable biology and meticulous care pathways, thereby potentially depressing observed recurrence risk relative to average practice.
2. A central threat to validity is differential staging intensity across procedures. Anatomical resections were accompanied by systematic nodal dissection, whereas wedge resections used nodal sampling "based on the surgeon's discretion." This leaves room for occult N disease being misclassified as N0, particularly in the 12% who underwent wedge resection; notably, three of ten total recurrences occurred after wedge resection. Even if the authors refrain from causal interpretation due to low counts, discretionary nodal sampling can bias the apparent prognosis of "node-negative" patients downward by moving some truly node-positive patients into the N0 stratum, thereby diluting the risk estimate that underpins the proposed policy change. A sensitivity analysis excluding wedge resections or restricting to patients with verified systematic nodal dissection would help quantify this bias.
3. The definition and ascertainment of recurrence combine histologic confirmation with multidisciplinary consensus in cases detected radiologically but not biopsied. While pragmatic, this composite endpoint risks incorporation and classification bias, mainly because the two centers used different surveillance schedules and modalities (e.g., MRI abdomen instead of CT in younger patients at one center), which may influence the probability and timing of detecting small, asymptomatic events. Without adjustment for center-level differences in surveillance intensity and imaging modality, heterogeneity in detection could either inflate or deflate recurrence incidence differentially across subgroups, challenging the comparability of cumulative incidence across the N0 and N-positive strata and institutions.
4. The handling of competing risks is broadly appropriate for estimating crude probability of recurrence; the Aalen–Johansen estimator with death as a competing event aligns with the clinical estimand. However, the manuscript asserts that "death due to TC would have been preceded by a detectable recurrence," and on that basis assumes that recurrence does not occur until detection. In real-world follow-up, particularly with staggered imaging, some patients may die of disease or disease-related causes without interval documentation of radiologic recurrence, leading to informative misclassification: latent recurrences can be absorbed into the competing event. This structural assumption biases the cumulative incidence downward if undetected recurrences occur between scheduled scans or after cessation of follow-up, and it also complicates the interpretation of the Fine–Gray subdistribution hazards if ascertainment depends on surveillance schedule intensity. A sensitivity analysis varying the detection assumption, or an illness–death multi-state approach, would better characterize this uncertainty.
5. The modeling strategy limits inference. The authors fit only univariable Fine–Gray models for lymph node status and tumor size. With ten total events, model parsimony is necessary; nonetheless, univariable estimates risk confounding by factors correlated with N-status, such as central versus peripheral location, procedure type (wedge vs segmentectomy vs lobectomy), Ki-67, mitotic count, and age. Even a constrained multivariable approach with penalization or propensity score weighting could help test the robustness of the node effect. As presented, the striking subdistribution hazard ratio for N-positivity (SHR 11.1) is accompanied by an extensive confidence interval (3.1–39.0), reflecting extreme imprecision and leaving the true magnitude uncertain. Conversely, the null finding for tumor size (SHR 1.7; 95% CI 0.2–13.3) is almost certainly underpowered and should not be overinterpreted as evidence of the absence of effect. These features argue for caution in translating the point estimates into practice recommendations.
6. Missingness and classification issues are insufficiently detailed. Thirteen patients are listed as Nx, but it is unclear how they were handled in the exposure definition for the Fine–Gray models that dichotomize nodal status as "yes vs no." Inclusion of Nx within the "no" category would bias estimates toward the null if any of these patients were node-positive but not sampled. Similarly, tumor location is missing in twenty-one patients, and Ki-67 is missing in four, yet there is no description of imputation strategies or complete-case analyses. A transparent accounting of missing data and a sensitivity analysis excluding Nx or using multiple imputation would strengthen credibility.
7. The endpoint strategy does not account for competing clinically relevant outcomes of surveillance beyond recurrence. The recommendation to cease imaging in node-negative patients is supported by an external modeling study of radiation-induced cancer risk under specific protocols, and by a survey from NSCLC surveillance describing downstream testing from false positives. However, the manuscript does not quantify potential benefits unique to this population, such as detection of second primary lung cancers or actionable non-carcinoid findings, nor does it recalibrate radiation modeling to the two-center schedules used here (which include MRI abdomen for younger patients at one center, potentially reducing dose). The net-benefit argument, therefore, relies on non-specific external evidence rather than an analysis of benefit–harm trade-offs in the present cohort. Incorporating a center-specific estimate of

PROCES FOR LUNGE NET KONTROL

Forundring/nysgerrighed

Undersøgelse - forskningsprojekt

Fremlæggelse kongres

Artikel

Guidelines ændres

ANBEFALING OG GUIDELINE

- Patienter med TC **uden lymfeknudemetastaser** behandlet med kurativt sigte har **meget lav risiko for recidiv** og **bør ekskluderes fra follow-programmer**.
- Patienter med lymfeknudemetastaser bør fortsat følges efter nuværende anbefalinger.
- Indført i DK (Uni-5)
- ENETS –lung task force