APPENDICES

Appendix I: Classification of discrepancies in diagnosis, stage and therapeutic advice after a second opinion and description of these discrepancies according to their potential major, minor and identical impact on patient outcomes

Appendix II: Case reports: figures
APPENDIX I

Classification of discrepancies in diagnosis, stage and therapeutic advice after a second opinion and description of these discrepancies according to their potential major, minor and identical impact on patient outcomes

Classification of criteria for Non-Small Cell Lung Cancer (NSCLC) [IKC]

General rules:
- If a patient fulfils the criteria of both changes with potential minor and major impact on patient outcome, the major change should count above the minor change
- If a patient fulfils the criteria of a change with potential major impact, then it doesn’t matter whether a patient is included in a trial, the fact that a patient fulfils the criteria of a change with major impact counts above trial inclusion
- If a patient doesn’t fulfil the criteria of a change with major impact and becomes included in a trial, then the patient’s outcome should be regarded as identical, and categorized according criteria 1 of the changes with identical impact on patient outcome.
- When multiple discrepancies are found in 1 patient, only the discrepancy with the most important potential impact is counted

Changes with potential major impact
(aimed at improvement of outcome by changed therapy)

1. inoperable ↔ operable
   a. surgery ↔ palliative chemotherapy/chemotherapy + sequential radiotherapy (RT)/expectative management/concurrent chemoradiation with curative intent
   b. no surgical resection after therapy induction
   c. inoperable (as a result of bad condition/Body Mass Index/Lung Function/high risk operation (e.g. in necrotic area)
2. palliative RT ↔ RT with curative intent
3. chemotherapy ↔ concurrent chemoradiation (and eventually resection)
4. treatment of brain metastases
   a. whole brain RT ↔ stereotactic RT (SRT)
   b. surgical metastasectomy ↔ SRT
   c. whole brain RT ↔ surgical metastasectomy
5. performing mutation analysis and its results:
   a. in case of positive EGFR mutation (+) → change with potential major impact
      i. EGFR + exon 19 → change with potential major impact
      ii. EGFR + exon 21 → change with potential major impact
      iii. EGFR + exon 20 (resistance to Tyrosine Kinase Inhibitors (TKI)) → change with potential identical impact
      iv. EGFR analysis later during treatment trajectory → does not count as a potential change
b. in case of negative EGFR mutation (−) and positive K-ras mutation (+) → check for other changes with potential impact and classify as a change with potential minor or identical impact

c. in case of EGFR mutation – and K-ras + and trial inclusion → change with potential identical impact

6. no chemotherapy ←→ chemotherapy
   a. also valid for: no biological ←→ biological (in case of registered biologicals)

7. prognostic staging
   a. based on clinical/pathological judgement and review that the diagnosis malignant should be changed in benign and vice versa
   b. based on clinical/pathological judgement and review that the diagnosis lung cancer should be changed in another cancer type
   c. based on clinical/pathological judgement and review that the carcinoma of unknown origin/diagnosis should be changed in lung cancer
   d. based on clinical/imaging judgement and review that stages (1 ←→ 2 ←→ 3 ←→ 4) should be changed
   e. based on clinical/pathological judgement and review that the diagnosis lung cancer type should be changed in another lung cancer type and vice versa
      i. SCLC ←→ NSCLC
      ii. SCLC/NSCLC ←→ trachea tumor
   f. based on clinical/imaging judgement and review that within stage 4, the type of metastases should be changed:
      i. in case of known metastases, a new localization of metastases is determined or rejected

8. change in extent of surgery
   a. lobectomy ←→ wedge excision
   b. lobectomy ←→ more extensive resection

9. RT with curative intent ←→ chemoradiation with curative intent

10. surgical resection ←→ resection with additional treatment modalities
    a. resection ←→ resection + neoadjuvant chemotherapy
    b. resection ←→ resection + neoadjuvant concurrent chemoradiation
    c. resection ←→ resection + adjuvant chemotherapy
    d. switch in the number of additional treatment modalities

11. RT with curative intent ←→ surgery

12. surgery ←→ endobronchial therapy

13. endobronchial therapy ←→ endobronchial therapy + additional treatment modalities

**Changes with potential minor impact**

1. minor changes aimed at improvement of care/quality of life
   a. no palliative RT (no therapy) ←→ palliative RT
   b. palliative RT ←→ palliative chemotherapy/biological (without a EGFR mutation)
c. no therapy/expectative management/supportive care therapy instead of suggested therapy (in case of stage 4/advanced disease with prior therapy with a number of chemotherapy lines whereby therapy has no impact anymore on survival, but exclusively on quality of life)
d. therapy switch within a palliative setting
e. switch of chemotherapy to biological and vice versa (in case of EGFR- and K-ras+ or -mutation)

2. addition or removal of a treatment modality within a treatment with the same intent or a palliative/supportive treatment setting
   a. palliative chemotherapy + sequential RT ↔ palliative chemotherapy
   b. palliative RT + palliative chemotherapy ↔ palliative RT
   c. palliative. RT+ palliative chemotherapy ↔ palliative chemotherapy
d. SRT ↔ neoadjuvant chemotherapy + SRT
e. addition of endobronchial therapy to chemotherapy within a palliative treatment setting

3. prognostic staging
   a. based on clinical/pathological judgement and review that the diagnosis of NSCLC subtype (adenocarcinoma/squamous cell/large cell/not otherwise specified) should be changed in another subtype
   b. based on clinical/pathological judgement and review that the diagnosis of a lung cancer type (NSCLC/carcinoid/unknown lung cancer type) should be changed in another lung cancer type
   c. based on clinical/pathological judgement and review that the diagnosis of carcinoid subtype (typical/atypical) should be changed in another subtype
d. based on clinical/imaging judgement and review that stages specifications (of stage 1/2/3) within the same stage should be changed (A ↔ B)

4. change in chemotherapy regimen
   a. gemcitabine/cisplatin → gemcitabine/carboplatin

5. change in the sequence of treatment modalities
   a. neoadjuvant chemotherapy + surgery ↔ surgery + adjuvant chemotherapy

6. the wish/request to be treated with chemotherapy within a trial is not granted

Changes with potential identical impact

1. change in therapy resulting in trial inclusion in the absence of a change with potential major impact
   a. any kind of trial
   b. trials with biologicals (provided that the EGFR mutation is negative)

NB: if there is already the suggestion that a patient could be enrolled in a trial and this suggestion is being granted, this does not count as a potential change.

2. the patient refuses the therapeutic advice of the expert center, is referred back to the referring hospital and receives therapy according to the first advice he received before referral

3. switch of unknown therapy to therapy

4. EGFR mutation of exon 20 = TKI resistance
Classification of criteria for Small Cell Lung Cancer (SCLC) [IKC]

Changes with potential major impact

[aimed at improvement of outcome by changed therapy]

1. addition of prophylactic cranial irradiation for SCLC with extensive disease
2. surgical resection of a residual tumor
3. expectative management/no chemotherapy $\leftrightarrow$ chemotherapy
   ii. after surgery
   iii. in case of recurrence/no recurrence and chance of cure

Changes with potential minor impact

1. expectative management/no chemotherapy $\leftrightarrow$ chemotherapy
   a. in case there is no chance of cure anymore
APPENDIX II

Case reports: figures
Benefit of a second opinion for lung cancer: no recurrent disease, but infection

Figure 1: CT scan at time of presentation: cavitation and multiple lesions

Figure 2: CT scan after open window thoracostomy with gauzes in situ

Figure 3: CT scan after muscle plasty of the serratus anterior muscle in the cavity
Benefit of a second opinion for lung cancer: intrapulmonary metastases or multiple primary tumors?

Figure 1: Computed tomography scan. Computed tomography scan at time of first presentation and after 6 cycles of chemotherapy. 1A shows a reduction of the lesion in the RUL. 1B shows an unchanged RML lesion and 1C shows a clear reduction of the LUL lesion.
Figure 2: Results of a-CGH analysis. Chromosomal rearrangements as detected by a-CGH analysis for biopsies of tumor tissue are shown (tumor tissue: epithelium, no selection of invasive or in situ tumor parts). On the y axis is the log2 tumor to normal ratio and on the x axis the chromosomal position. Gray dots are an average of 5 array measurements, because a moving average of 5 was used for each of the 3 plots. Gains and losses are positive and negative log2 ratio respectively. The quality of the 3 plots are variable, reflecting the use of formalin fixed paraffin embedded clinical material specimens.
A. Wedge excision apex left upper lobe: papillary adenocarcinoma
B. Wedge excision right middle lobe: adenocarcinoma in situ (AIS)
C. Lobectomy material of the right upper lobe: mixed papillary adenocarcinoma/AIS
Non-tumor DNA of this patient served as reference for each tumor. The arrows and corresponding signs (++, +, N and C) show the most obvious patterns of gains and losses in the chromosomes 1, 8 and X (number 23), with ++ representing a whole chromosomal arm gain, + a partial chromosomal arm gain, N no chromosomal aberrations and C complex chromosomal band of gains and losses. Plot B is of marginal quality and hence, difficult to interpret. However, as shown by the arrows in the 3 plots, differences in gains and losses can be observed. The first arrow indicates no chromosomal aberrations in chromosome 1 in plot B versus a complex change in plot A and a partial arm gain in plot C. The second arrow also shows no chromosomal aberration of chromosome 8 in plot B versus a complex change in plot A and a whole chromosomal arm gain in plot C. The third arrow indicates a gain of the entire X-chromosome in plot B, much like the X-chromosome gain in the sample of plot C, in contrast with the partial X-chromosome gain in plot A. Gross chromosomal differences are thus detected in the sample of plot B despite the marginal quality and it is therefore reasonable to conclude that these differences support the assumption of different tumor origins. All array data are available in the Gene Expression Omnibus (GEO) database, under accession number GSE42377.

**Benefit of a second opinion for lung cancer: no metastasis to the kidney but a synchronous primary renal neoplasm**

![Figure 1](image.png)

**Figure 1.** a Infiltrating glandular structures composed of atypical columnar cells with prominent nucleoli in the resection of thoracic vertebra 10, histologically consistent with adenocarcinoma of the lung. The papillary growth pattern is less prominent than in the papillary renal cell carcinoma (HE). After therapy, only a small remnant of tumor was found in a background of sclerotic and reactive changes. b Immunohistochemistry for TTF-1 is positive in the adenocarcinoma of thoracic vertebra 10, consistent with a primary localization of the lung. c Tubulopapillary structures composed of uniform cuboidal cells with unsuspicious round nuclei, without atypia and foamy macrophages in the papillary cores. Histologically consistent with primary papillary renal cell carcinoma type 1 in renal biopsy (HE). d Immunohistochemistry for TTF-1 is negative in the papillary renal cell carcinoma, confirming a second primary tumor.
Benefit of a second opinion for lung cancer: from metastatic disease to resectable lung cancer with sarcoid-like reaction

Figure 1: PET and CT scan. PET (alternation corrected and non-alternation corrected) and low dose CT images showing a pattern of bilateral hilar and mediastinal uptake in the lymph nodes, characteristic of sarcoid-like reaction, close to a parenchymal abnormality highly suspicious for a lung cancer in the left upper lobe.

Figure 2: Non-caseating granulomas in one of the mediastinal lymph node. The granulomas are well formed and consist primarily of epitheloid histiocytes with multinucleated giant cells. These granulomas are characteristic of sarcoidosis lymphadenopathy. The pan-cytokeratin staining was negative, excluding a sarcoid-like reaction to tumor cells (not shown).
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Romane Milia Schook (1984) was born in Die (France) and was raised on a farm in the Drôme until she moved to the Netherlands with her family at the age of 14. After mastering the Dutch language, she completed her high school education (VWO, cum laude) in 2003 at the Berlage Lyceum in Amsterdam, after which she immediately commenced her study of Medicine at the Vrije Universiteit. In December 2004, Romane started doing research as a student assistant to Prof. Dr. P.E. Postmus at the Department of Pulmonology of the VU Medical Center. Gradually, her student research grew into a PhD program for which she temporarily postponed the internships of her Medical degree in 2008. After one year of full-time PhD research, she started her internships and continued her PhD in part-time. In May 2011 she graduated as a medical doctor (cum laude) and recommenced her full-time PhD research. Romane started her training to become a general practitioner in March 2014 at the HoVUmc and completed her PhD thesis during the first year of her traineeship. Romane is married to Nabil and the proud mother of Amina (2013).