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Chemotherapy followed by surgery on the basis of biomarker examination for initially unresectable non-small cell lung cancer (NSCLC) patients

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Background-1

- It has been reported that the effectiveness of new-generation cytotoxic agents for advanced NSCLC is equivalent.
  (*N Engl J Med.* 2002;346:92-8.)

- It has been reported that pemetrexed and S-1 are not inferior to first-line chemotherapy for advanced NSCLC.
  (Clin Oncol. 2008;26:3543-51. *J Clin Oncol.* 2010;28:5240-6.)

- So, an appropriate chemotherapy menu (using Taxane, Pemetrexed, S-1 and Gemcitabine) can be selected for any individual on the basis of biomarker status, without any disadvantage.

Background-2

- We reported that patients with cN2, 3 NSCLC with simultaneous low expression of excision repair crosscomplementing 1 (ERCC1) and class III β-tubulin (tubulin) were promising candidates for surgery after carbo-taxane chemoradiotherapy.

- The expression of tubulin, ribonucleotide reductase M1 (RRM1) and thymidylate synthase (TS) was significant prognostic factor in those cases (2012, STS annual Meeting).

- In our last study, there were a number of limitations. Firstly, it was retrospective and the biomarker status indicative of a pathologically complete response could not be identified.

- Secondly, all patients in the last study underwent carboplatin-taxane induction chemotherapy. The real significance of TS and RRM1 status on predicting patients' survival was unclear.

Purposes

- Although there has been considerable progress with targeting therapy and new-generation cytotoxic agents, surgery is still one of the best potentially curative therapeutic options for NSCLC.

- If best chemotherapy menu for an individual can be selected from biomarker status of tumor, salvage operation for cure may be possible.

- We conducted a prospective study. We tried chemotherapy on the basis of biomarker examination for initially unresectable NSCLC patients. For patients who exhibited good PR or CR, operation was tried.

Patients and Methods

- Twenty-five patients with pathologically proven NSCLC initially diagnosed as unresectable were enrolled (Oct. 2010 to June 2012).

- The reasons for unresectabilities were 13 bulky N2-N3, 2 chest wall and vertebral invasion, 2 tracheal invasion, 2 single brain metastais, 2 lung metastasis, 2 poor lung function, 1 adrenal metastasis and 1 atrial invasion.

- We tried chemotherapy on the basis of biomarker examination for initially unresectable NSCLC patients. For patients who exhibited good PR or CR, operation was tried.

Strategy for each unresectable reason

- For bulky N2-N3 diseases, mediastinoscopy was done for pathological confirmation.
- For single treatable brain metastasis, γ-knife was performed and complete response was confirmed.
- For lung metastasis, VATS biopsy was performed to confirm pathologically complete response.
- For adrenal metastasis, laparoscopic resection of affected adrenal was performed.

Criteria for drug selection

1. Regardless of biomarker status, application of platinum doublet therapy is mandatory.
2. Patient with low β-tubulin carcinoma will receive platinum and docetaxel.
3. Patient with low TS non-squamous cell carcinoma will receive platinum and PEM.
4. Patient with low TS squamous cell carcinomas will receive platinum and S-1.
5. Patient with low RRM1 carcinoma will receive platinum and gemcitabine.
6. If possible, bevacizumab will be administrated in patients with non-squamous cell carcinoma.
7. If possible, concurrent thoracic irradiation (50 Gy).

Patient characteristics

Characteristic	No. of patients	Percentage(%)
Total no. of patients	25	100
Age		
Median	66.0	
Range	34-78	
Gender		
Male	21	84.0
Female	4	16.0
Histology		
Adenocarcinoma	12	48.0
Squamous cell carcinoma	11	44.0
Other	2	8.0
Clinical stage		
Stage IIIA	14	56.0
Stage IIIB	5	20.0
Stage IV	6	24.0

Antibodies and adjustment

a mouse monoclonal antibody for ERCC1 diluted at 1:200.
(FL-297; Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA)
ERCC1-high tumor: positive staining tumor cells > 30%

a rabbit monoclonal antibody for class III β-tubulin diluted at 1:500
(EP1569Y; Epitomics Inc., Urulingame, CA, USA)
class III β-tubulin -high tumor: positive staining tumor cells > 30%

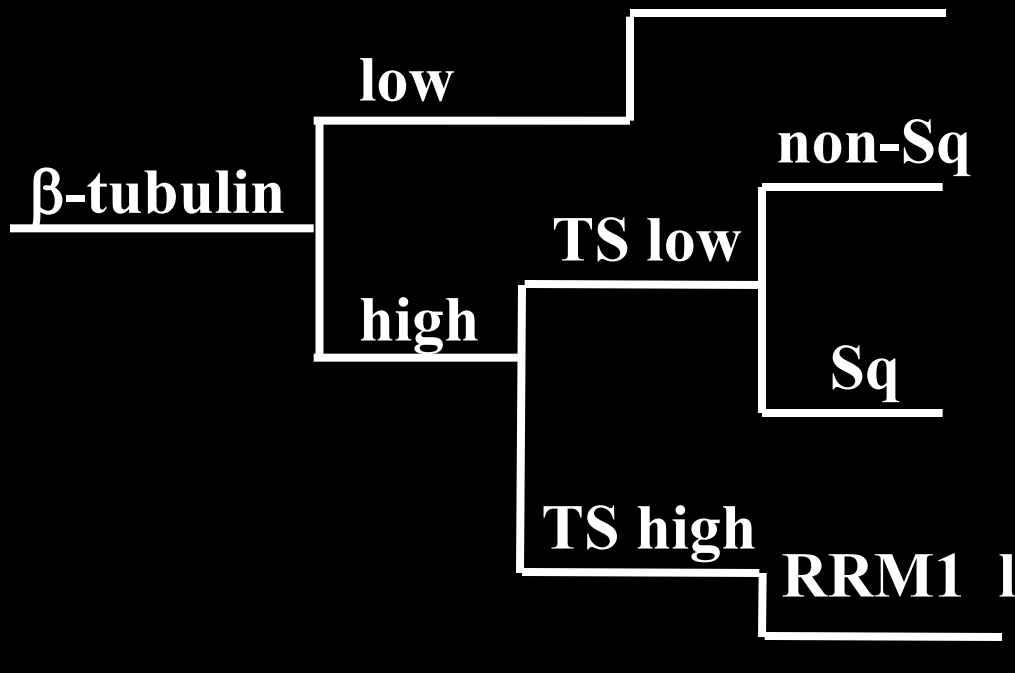
a rabbit monoclonal antibody for TS diluted at 1:500
(kindly provided by Dr M Fukushima)
TS-high tumor: HSCORE in a given specimen > 30
HSCORE= $\sum$(I x PC) I: staining intensity ; PC: percentage of cells at each intensity

a rabbit polyclonal antibody for RRM1 diluted at 1:500
(10526-1-AP; Protein Tech Group, Chicago, IL, USA)
RRM1-high tumor: positive staining tumor cells > 40%

Results-1

Characteristic	No. of patients	Percentage(%)
Therapeutic menu		
Platinum + DOC + RTx	12	48.0
Platinum + PEM + RTx	4	16.0
Platinum + DOC + bevacizumab	3	12.0
Platinum + S-1 + RTx	3	12.0
Platinum + PEM + bevacizumab	2	8.0
Platinum + S-1	1	4.0
Response to induction therapy		
Partial response	21	84.0
Stable disease	3	12.0
Progressive disease	1	4.0
Method of surgical resection		
Lobectomy or bilobectomy	19	76.0
Pneumonectomy	2	8.0
Without surgery	4	16.0
Pathological effect of induction therapy		
Complete response	4	19.1
Major response	10	47.6
Minor response	7	33.3

Results-2



Regimen	patient No. of surgery
Platinum + DOC	(11/15)
Platinum + PEM	(6/6)
Platinum + S-1	(4/4)
Platinum + GEM	(0/0)

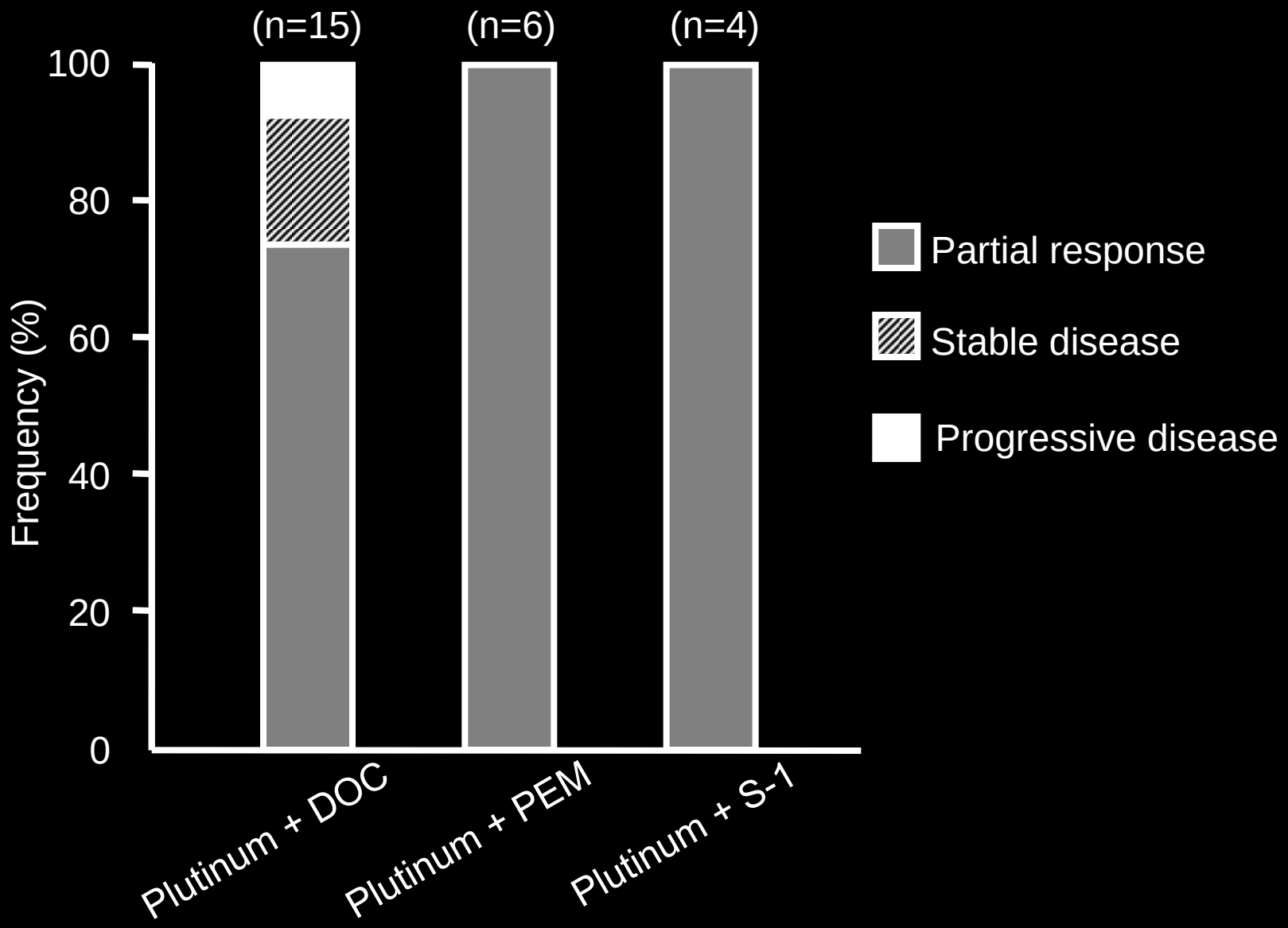
Addition of bevacizumab in non-Sq if possible (5/5)

Concurrent radiation (50 Gy) (15/19)

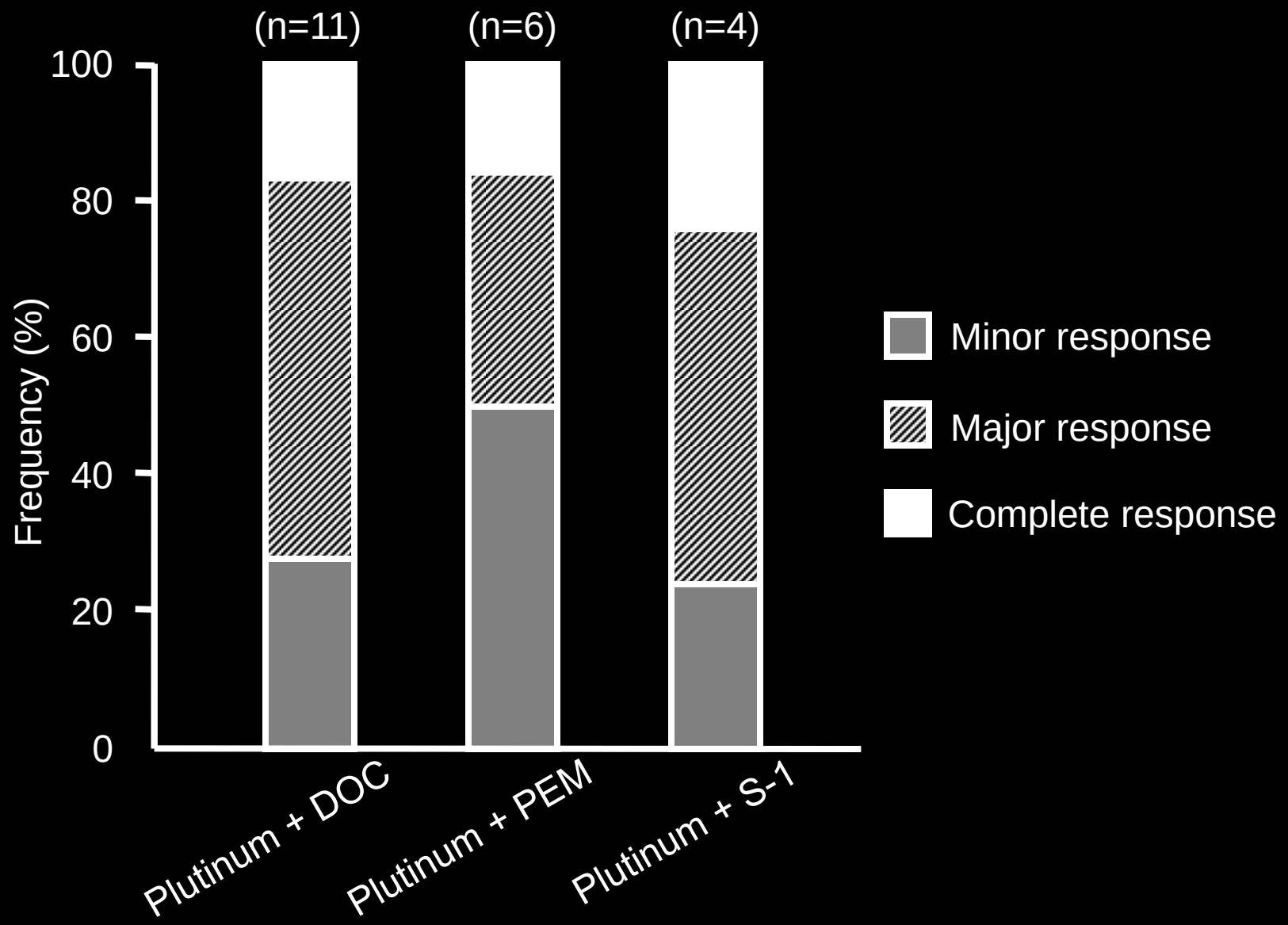
Results-3

Characteristic	No. of patients	Percentage(%)
Changes of biomarker		92.9
all	1	
three	9	
two	5	
one	2	
Adjuvant chemotherapy	10	
Platinum + DOC	3	30.0
Platinum + S-1	2	20.0
S-1	2	20.0
bevacizumab	2	20.0
Platinum + PEM	1	10.0
Reccurenece	9	
primary site	3	33.3
lung	3	33.3
brain	2	22.2
adrenal	1	11.1

Response to induction chemotherapy

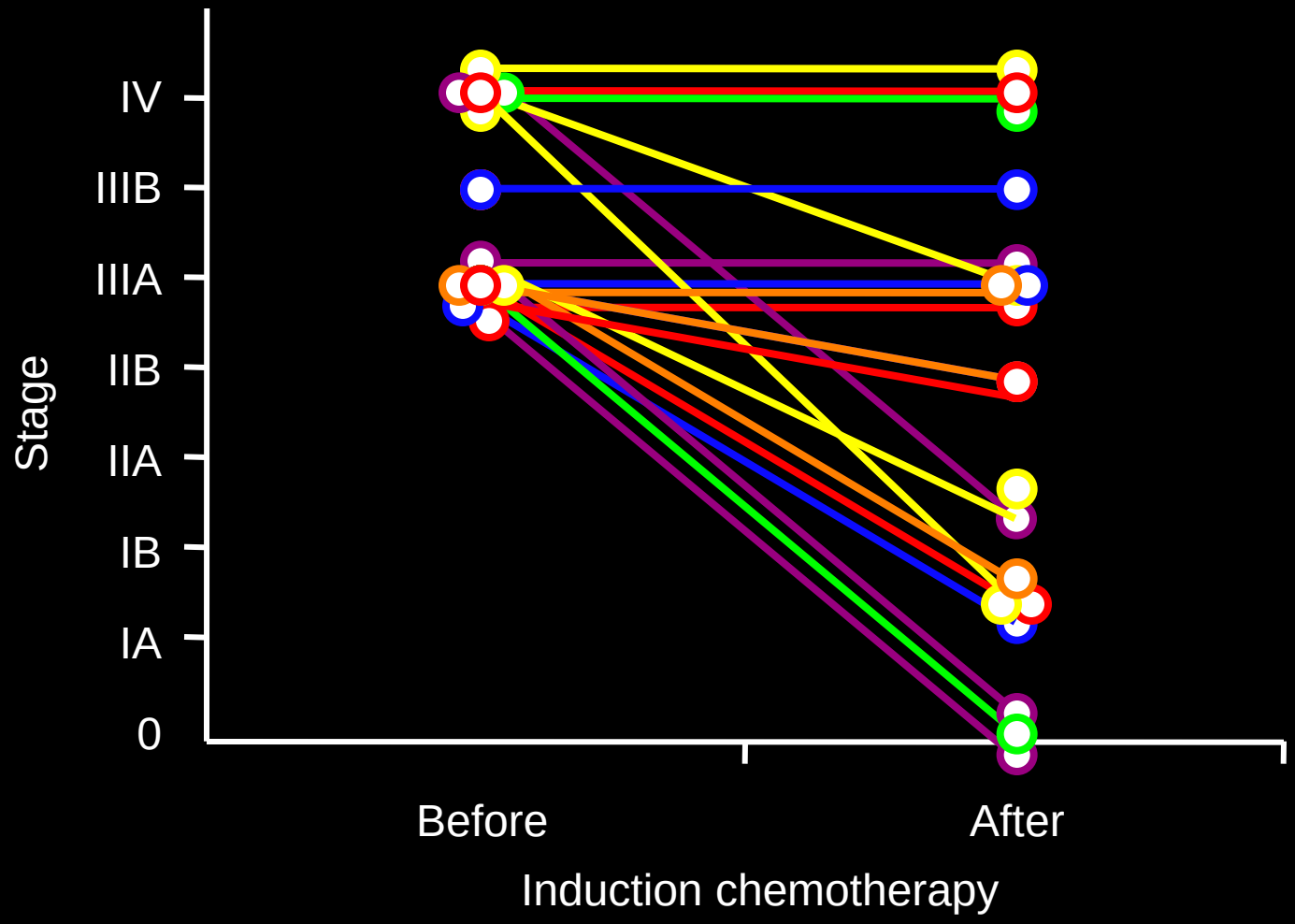


Pathological effect of chemotherapy

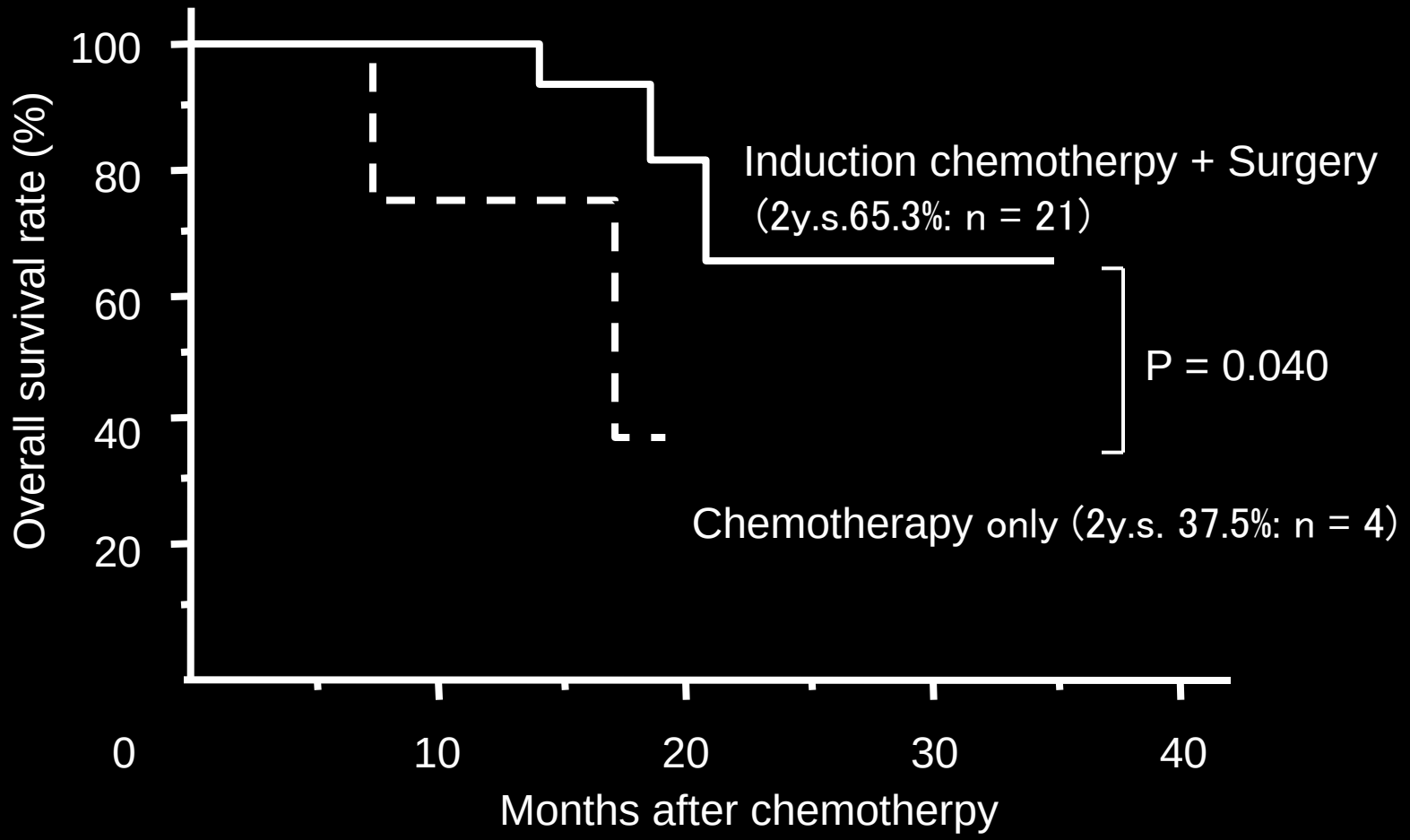


Stage change after induction chemotherapy followed by surgery

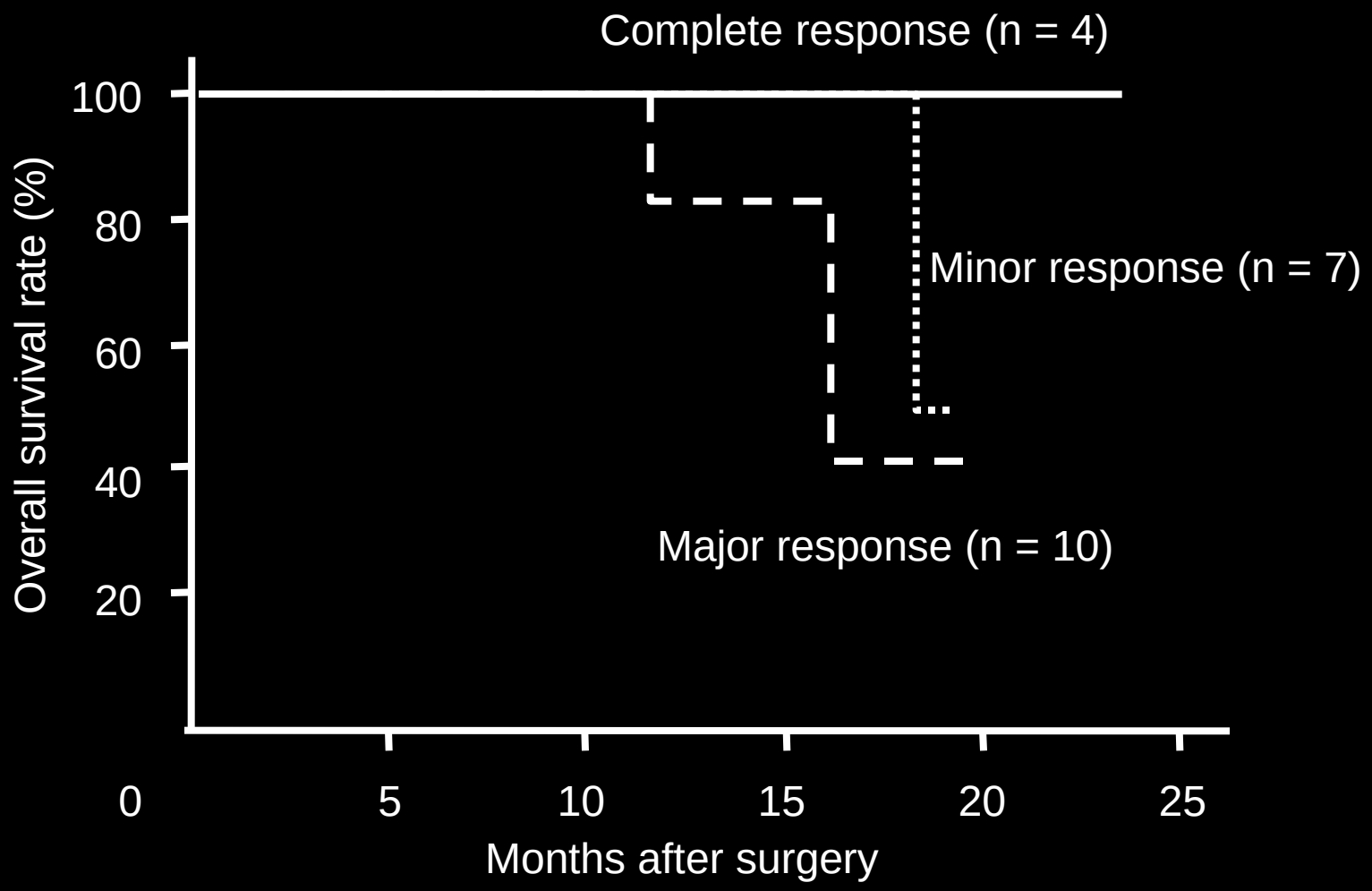
Stage down: 16/21(76.2%)



Overall survival of 25 patients after induction chemotherapy



Overall survival of 21 patients treated by surgery after induction chemotherapy in relation to pathological effect.



Summary

- 25 initially unresectable NSCLC patients received chemotherapy on the basis of biomarker status of tumor.
- Twenty-one (84%) of the 25 patients with PR underwent complete resection successfully without major morbidity or morality.
- With regard to the stage, 16 (76.2%) out of 21 operated patients achieved stage down after chemotherapy.
- The 2-year survival rate was 58.7% for the 25 patients overall, 65.3% for patients underwent surgery after chemotherapy and 37.5% for patients without surgery.

Limitations

- This is a small number study and observation time is so short.
- Canadian consensus recommendation reported that there is insufficient evidence of ERCC-1, beta-tubulin III and RRM1.
- Booton et al. reported that ERCC-1 expression is not associated with response and survival after platinum-based chemotherapy regimens in advanced non-small cell lung cancer.
- Gomez-Roca et al. reported differential expression of biomarkers in primary non-small cell lung cancer and metastatic sites.

Conclusions

- Chemotherapy followed by surgery on the basis of biomarker examination appears to be a promising strategy for patients with initially unresectable NSCLC, who otherwise might have a poor prognosis.

- This tailor-made strategy may open a new avenue for treatment of patients who were previously considered incurable.