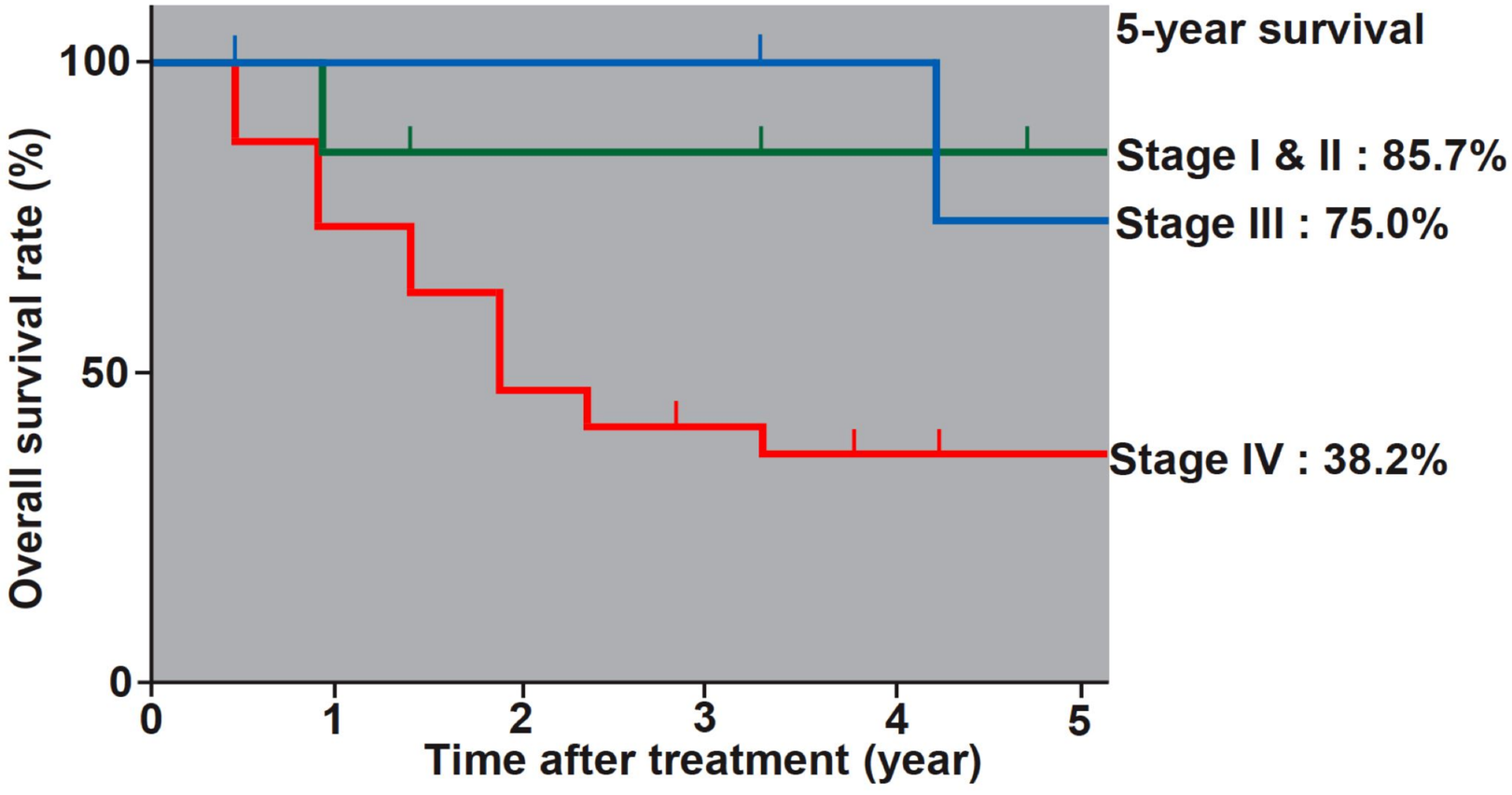
Immunotherapy for patients with head and neck cancer

'Translational research'

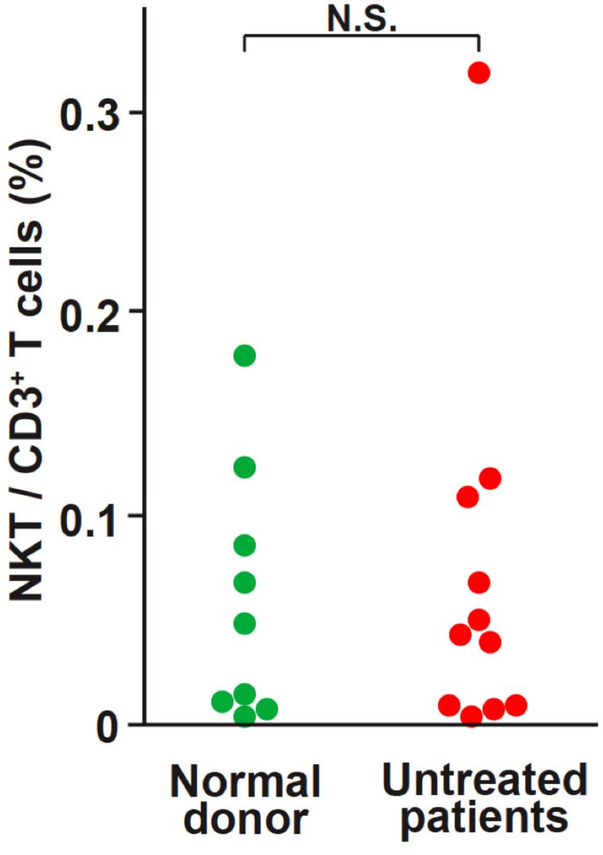
Characteristics of head and neck cancer

1. **The management of most patients with advanced head and neck cancer involves a combination of surgical therapy, chemotherapy and radiation therapy. Despite this, their prognoses are still poor. In addition, the patient's QOL is significantly impaired by the treatment. Therefore, immunotherapy is desirable.**
2. **The peripheral NKT cell populations of patients with head and neck cancer are the same as that of a normal donor.**

Overall survival rates of patients with hypo-pharyngeal cancer who received treatment at Chiba U. Hospital



A comparison of peripheral NKT cell populations between a normal donor and untreated head and neck cancer patients.



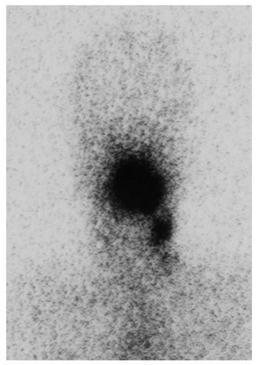
Characteristics of head and neck cancer

3. **The administration of antigen-specific dendritic cells into nasal submucosa enable the lymphocytes in the regional lymph nodes to sufficiently activate.**

48 hrs after injection of In^{111}-labeled dendritic cells into nasal submucosa

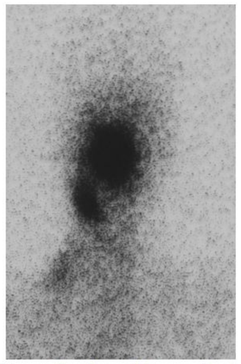
Front view

Case 1



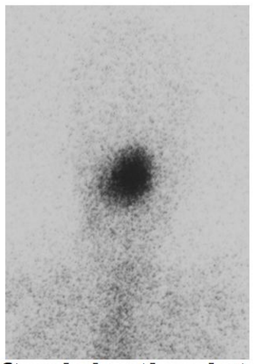
After injection into left nasal submocosa

Case 2



After injection into right nasal submocosa

Case 3



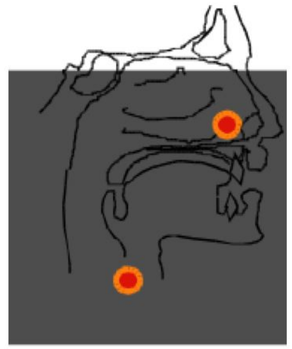
After injection into right nasal submocosa

(The patient has received right neck dissection)

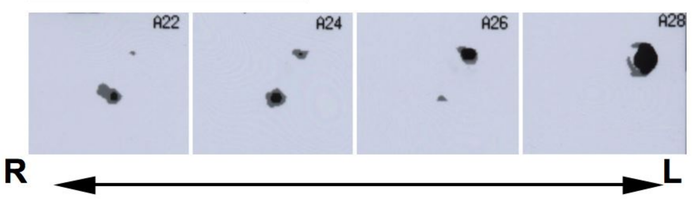
Indium^{111} labeled DCs

Sagittal sections

Case 2: Injection into right nasal submucosa



Indium was accumulated at the injection site and the regional lymph nodes.



4. **The blood supply of most head and neck cancers is provided by a terminal artery, therefore selective intra-arterial infusions are widely utilized.**

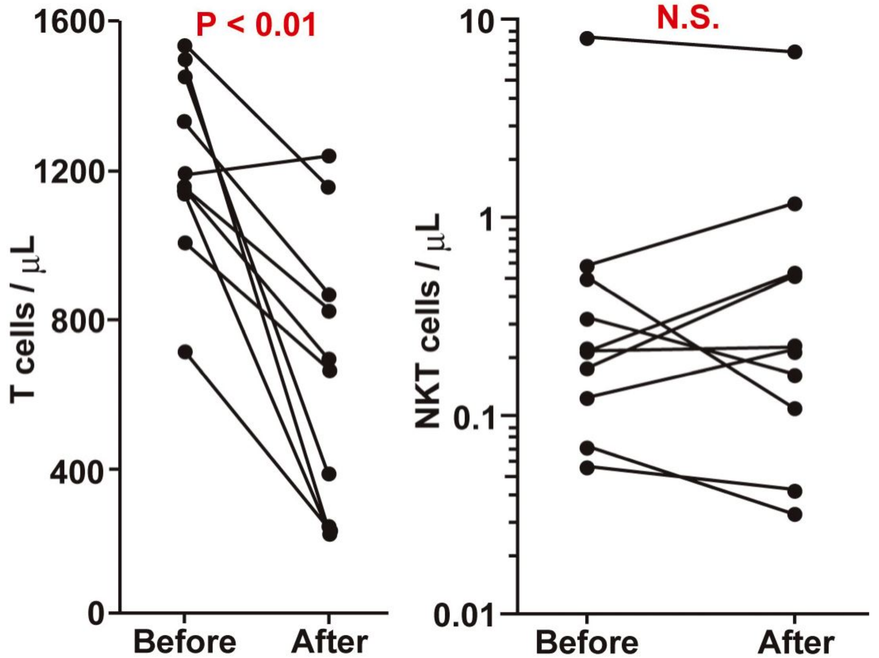
5. **It is easy to monitor the immunological responses with tumor tissue.**

Characteristics of head and neck cancer

6. Radiation therapy did not reduce the populations of peripheral NKT cells in patients with head and neck cancer.

Methodology: Peripheral blood samples were collected from 10 patients with head and neck cancer who were receiving radiation therapy, and absolute T ($CD3^+$) and NKT cell ($V\alpha24^+V\beta11^+$) numbers were analyzed using flow cytometry.

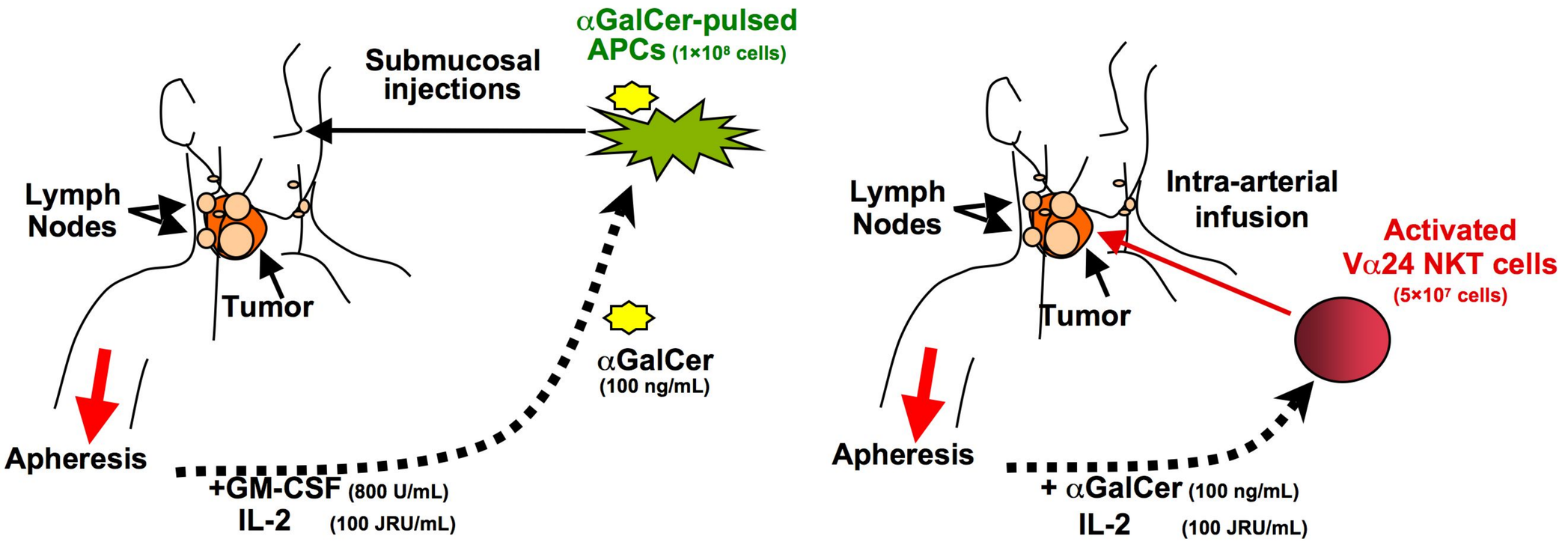
Case	Tumor site	T	N	M	Dose (Gy)	Area (cm^3)
1	Oropharynx	4	2c	0	60	400
2	Oropharynx	4	2b	0	46	378
3	Maxillary sinus	4	0	0	50	64
4	Larynx	4	2c	0	60	410
5	Tongue	3	2c	0	50	306
6	Hypopharynx	3	2b	0	60	306
7	Tongue	2	2b	0	60	264
8	Maxillary sinus	4	0	0	46	400
9	Maxillary sinus	4	0	0	50	119
10	Paranasal sinus	3	0	0	64	80



The absolute numbers of NKT cells in peripheral blood were maintained during radiation therapy, while T cells decreased significantly.

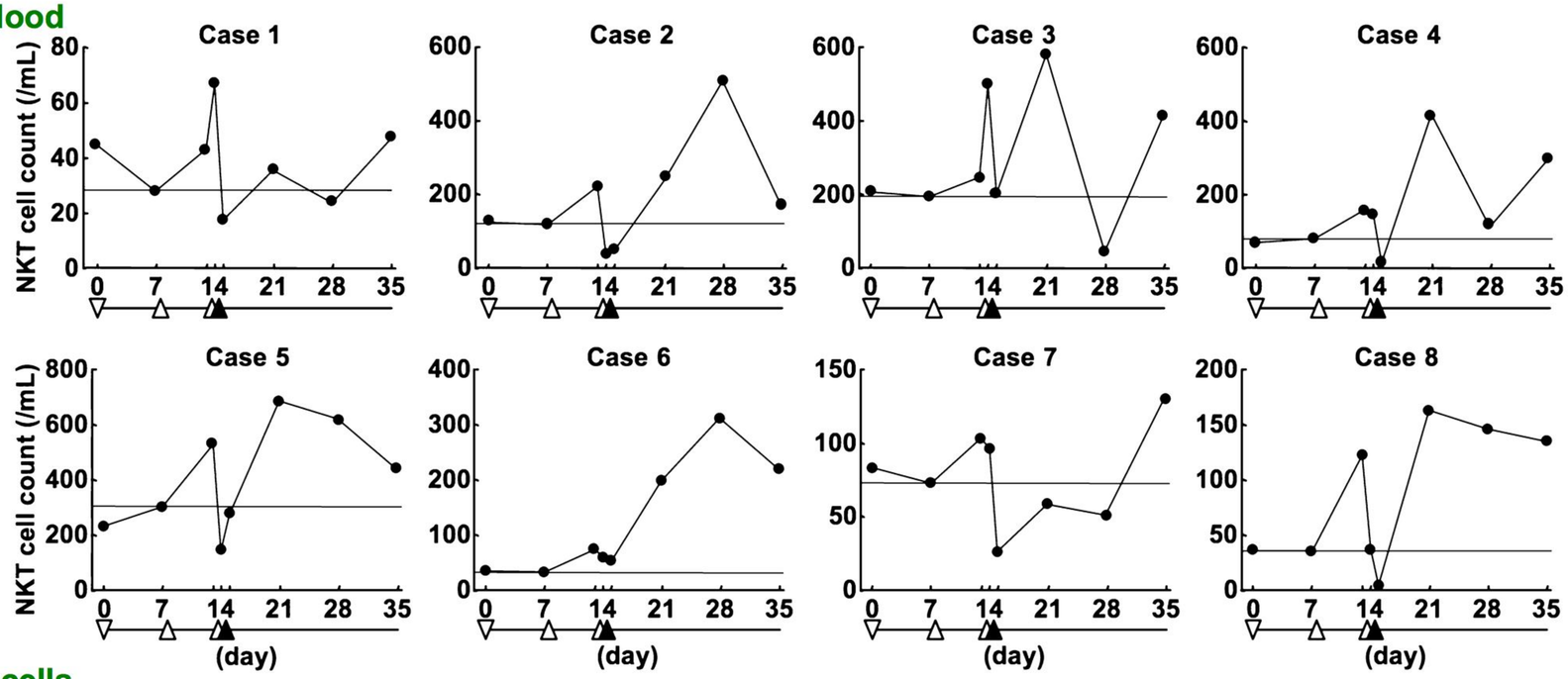
Study design

Primary endpoint : To detect the NKT cell-specific immune responses
Secondary endpoints: To confirm the safety profile
: To validate the antitumor effect

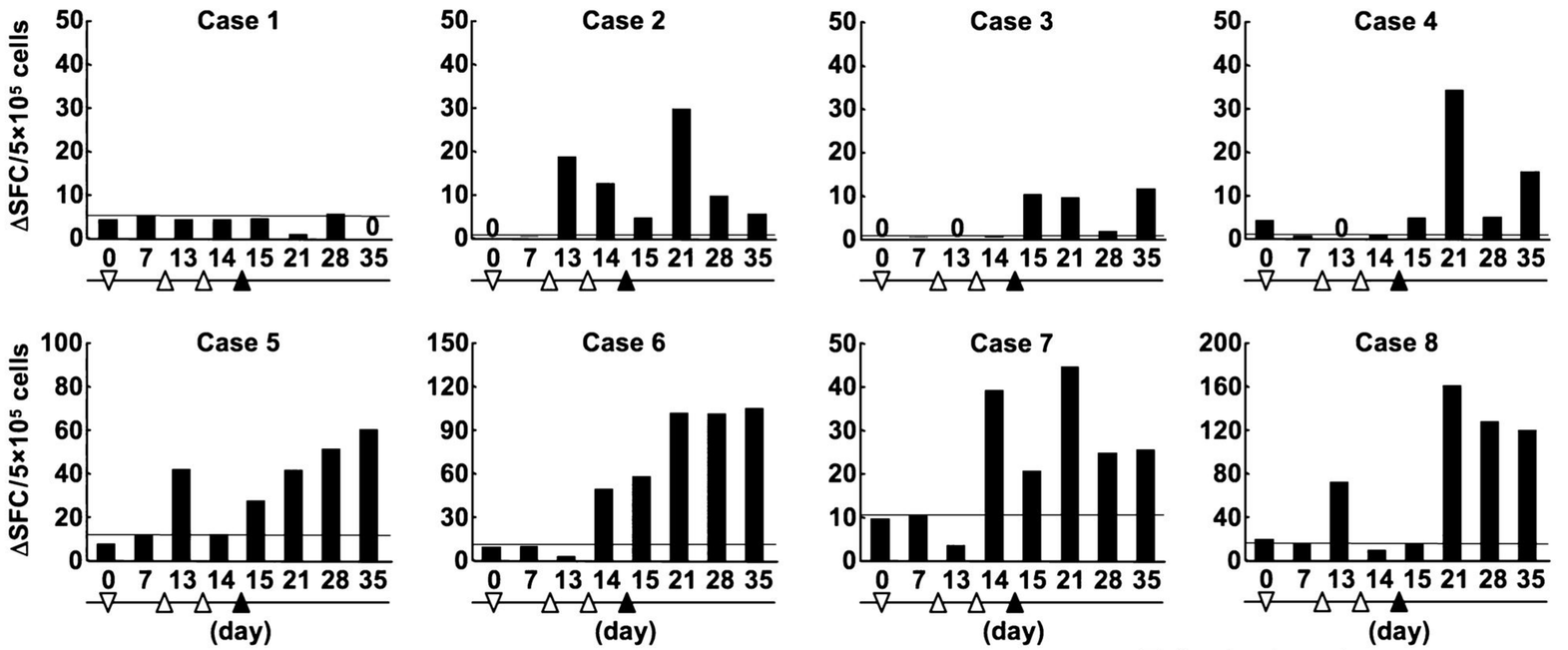


Immunological assays of peripheral blood samples

Absolute NKT cell count in peripheral blood



IFNγ producing cells after NKT cell-specific stimulation



Seven of eight patients (87.5%) appeared to have systemic NKT or NK cell-specific immunological responses initiated by the treatment.

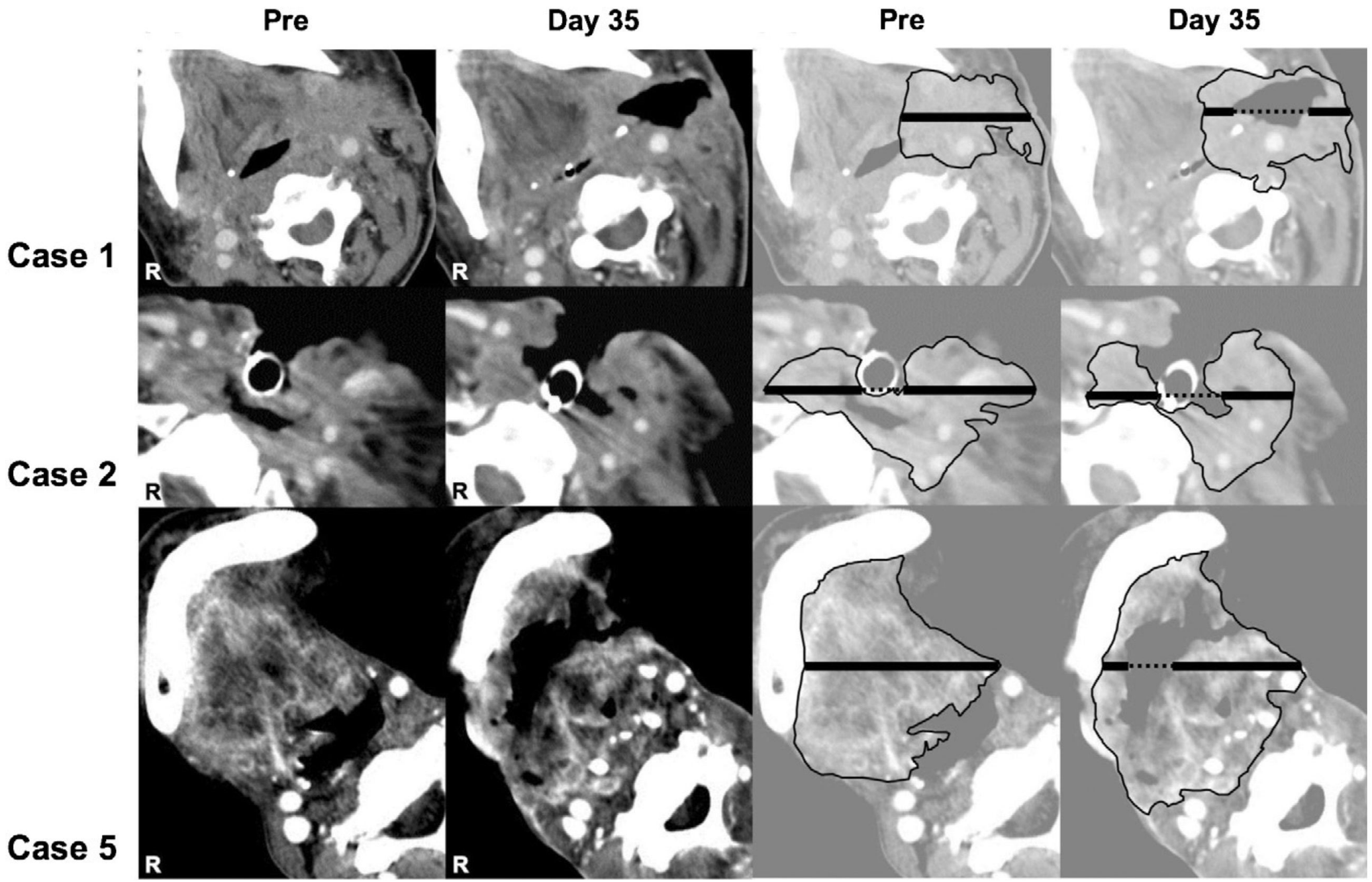
Observed adverse events and clinical response

Case	Adverse event			Clinical course	Tumor size (%)
	Grade 1	Grade 2	Grade 3		
1	Lymphopenia		Fistula (Pharynx)	PR	48
2	Lymphopenia	Fever		PR	65
3	Pain (external ear)			SD	104
4	Fever Headache			SD	109
5	Fever	Dehydration, pain (oral cavity)		PR	65
6	Fatigue Dizziness			PD	125
7	Pain (oral cavity)	Pain (back)		SD	104
8	Fever Fatigue			SD	110

PD, progressive disease; PR, partial response; SD, stable disease.

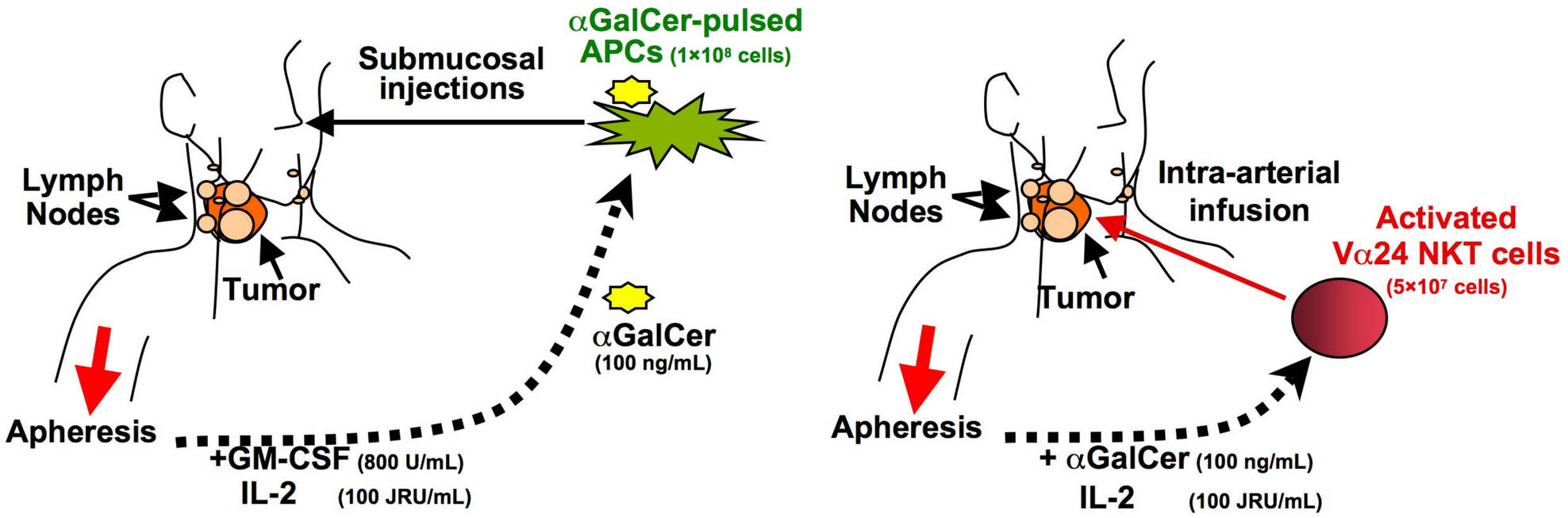
No major toxicity or severe side effects were observed.
Three patients (1, 2, and 5) showed a PR; four had SD; and one patient had a PD.

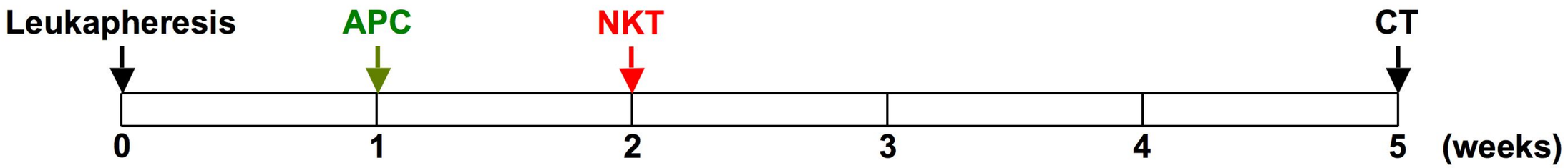
CT images of three PR cases



Study design

Primary endpoint : To validate the antitumor effect
Secondary endpoints: To confirm the safety profile
: To detect NKT cell-specific immune responses in peripheral blood and cancer tissue





Observed adverse events and clinical response

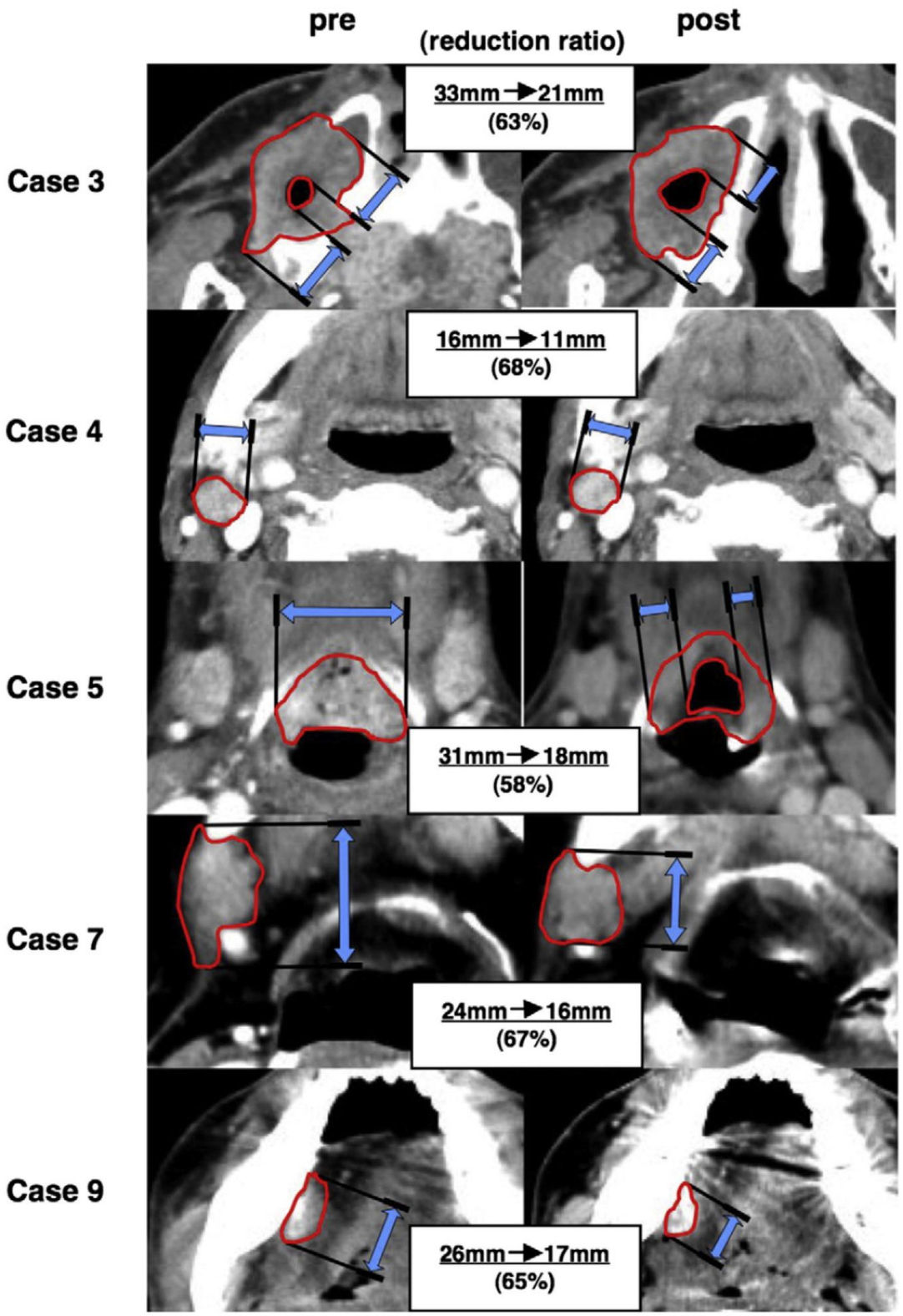
Case	Adverse events			Clinical effect	Pathological effect [a]
	Grade 1	Grade 2	Grade 3		
1	Mood alteration	Anemia Pneumothorax		SD	Ef.1a
2	Fatigue	Fever Lymphopenia		SD	Ef.1a
3	Fatigue			PR	Ef.1a
4	Anemia			PR	Ef.1b
5	Fatigue			PR	Ef.0
6				SD	Ef.1a
7	Hemoglobin Lymphopenia	Lymphopenia		PR	Ef.1a
8		Lymphopenia		SD	Ef.0
9	Lymphopenia	Anemia Lymphopenia		PR	Ef.1a
10		Anemia		SD	Ef.1a

PR indicates partial response; SD, stable disease; PD, progressive disease.

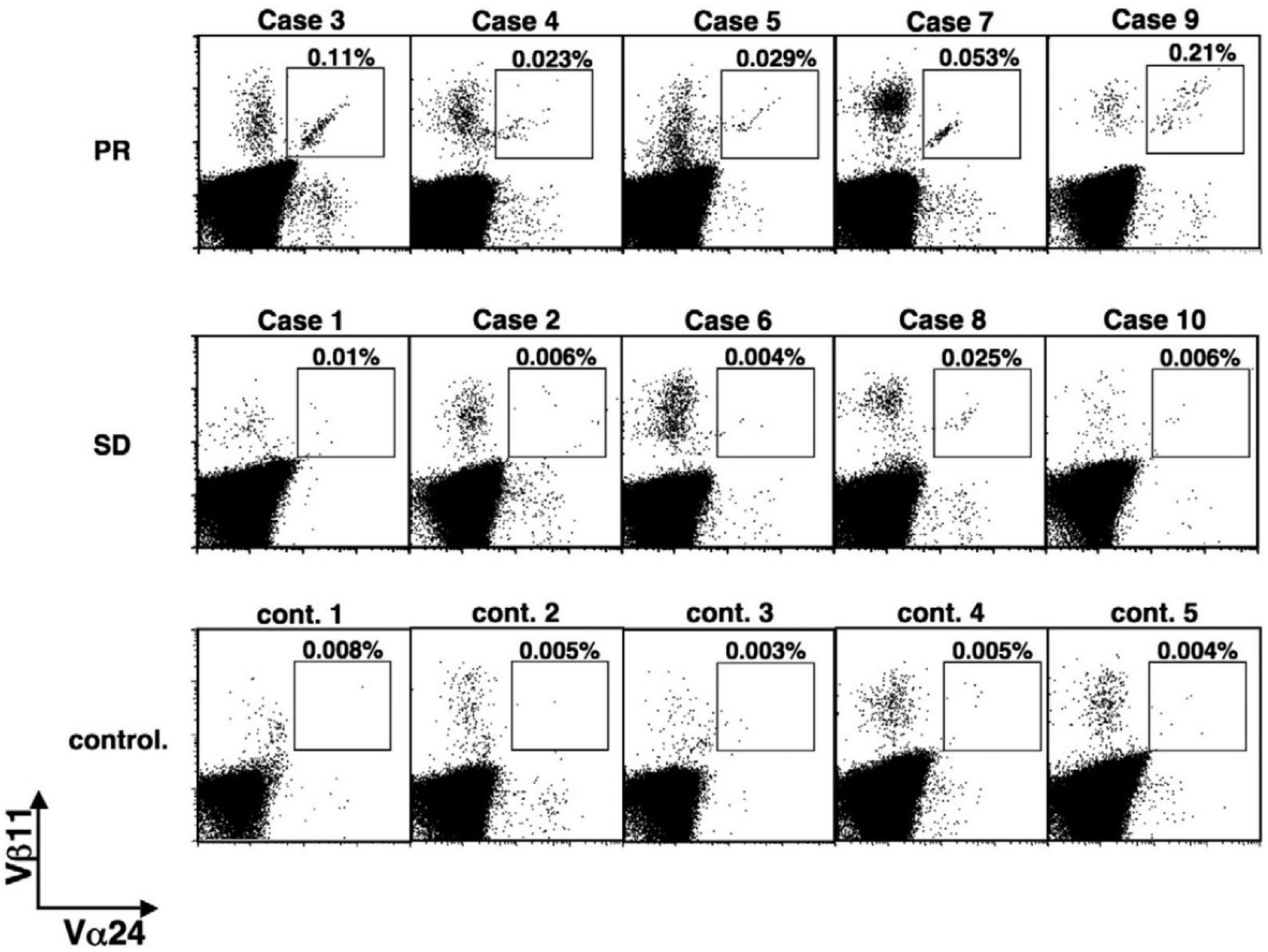
[a] Ef.0; Whole cancer cells are alive. Ef.1a; More than 2/3 of cancer cells are alive. Ef.1b; 1/3–2/3 of cancer cells are alive.

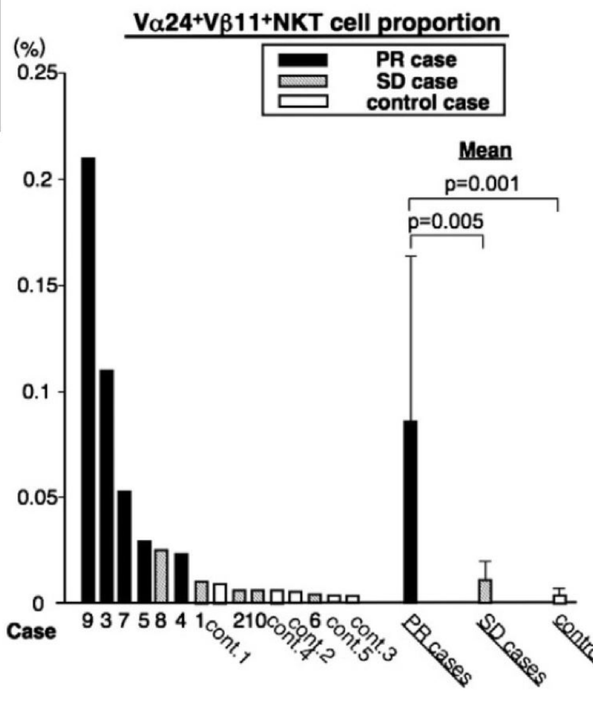
No major toxicity or severe side effects were observed.
Five patients (3, 4, 5, 7 and 9) showed a PR and five had SD.

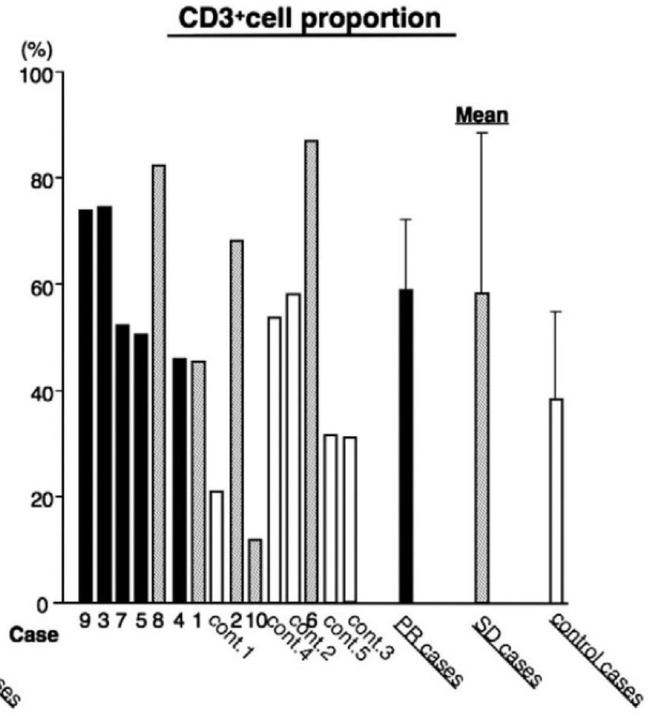
CT images of five PR cases



Immunological monitoring of TILs







The frequency of NKT cells in resected tumors was analyzed by flow cytometry and compared with those in a control group. More NKT cells were infiltrated into tumor sites in PR cases than that in SD ($p<0.005$) and control cases. The percentages of $CD3^+$ cells in PR and SD cases were almost the same, but were clearly higher than in control cases.