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Abstract

Tissue uptake of C-11 labelled methionine is evaluated in lung cancer patients using a positron emission tomography. Accumulation in cancer tissue resulted clear visualization of tumours in all cases. As lung count is much affected by tissue density, uptake is corrected for it using transmission scan data. C-11 count in the lung per unit weight is found to have initial clearance slope and showed some uptake of methionine in the later phase.

Introduction

Large fraction of ^{11}C-methionine is incorporated into protein 20 to 45 minutes after injection[1,2] and the rate of its uptake correlates to protein synthesis level of the tissue.[2] We already reported increased uptake of the substance in lung cancer nodules[3] but apparant tumour contrast from the lung might result from the density difference of the two tissue. Here we report the comparizon of methionine uptake between lung and tumor tissue corrected for the tissue density and blood volume.

Methods

Carbon-11 is obtained by bombering N_2 with 18 MeV proton accelerated in the Tohoku University cyclotron. ^{11}C-methionine is then synthesized using house-made automated ^{11}C-methionine synthesize unit.[4] After purity check and sterilization, 10-15 mCi of methionine is injected intravenously into subjects. Positron tomograms are obtained every 2 to 10 minutes after injection using ECAT II (EG & G Ortec, U. S. A.). Blood volume (BV) of the tissue is measured using ^{11}CO gas as a tracer. By referring transmission and blood volume data, total tissue density (TTD) and extravascular tissue density (EVD) of the lung is calculated according to Wolmer et al.[5] Extra-vascular methionine deposit in the lung (true methionine uptake, TMET) is measured by subtracting ^{11}CO count from ^{11}C-methionine images using radioactivity of the heart in both images as the normalization point.

The density-corrected methionine uptake (True MET uptake/weight, TMET/W) is calculated by division of the TMET image by tissue density image (Figure 3).

Uptake of isotope is expressed by the differential absorption ratio[6] (DAR) using below formula that corrects amount of isotope injected and patients' body weight.

$$DAR = Ct * Bw / (Ci * Cf * T)$$

where Ct : ECAT count/g, Ci : injected isotope in mCi
Cf : calibration factor between ECAT count and mCi
Bw : body weight, T : scan time

C-11 CO_2 in expired air is trapped to assess methionine metabolism using sodalime and counted by an ionization chamber (Capintec Inc. USA).

SUBJECTS

Four patients with lung cancer (squamous cell carcinoma, cytologically proved by bronchoscopical brushing) are studied. All are male with age ranging from 56 to 78 years old.

DETECTOR RESPONSE CHECK

Count linearity of transmission mode of our ECAT system is checked using sponges of various water content. ECAT measured their density in linear manner (Fig. 1). Emission mode response is checked using ^{11}C solution and its decay is followed. The response is found also satisfactorily linear (Fig. 1). Therefore transmission and emission count can be compared each other without any correction function.

CASE STUDY

<u>case 1</u>

K.Y. 62 y.o. male, squamous cell lung cancer.

He was found to have a nodule in left B_{1+2} lobule and diagnosed as above (Fig. 2). PCT studies shows remarkable MET uptake both in the tumour and subaortic lymph node. The uptake is due to extravascular tissue deposit as blood volume in the tumour in small (Fig. 3). The true MET uptake with tissue density correction shows higher count in the tumour than in the neighboring lung. The tumor lung ratio of DAR(30) is 1.1.

case 2

H.O. 78 y.o. male, squamous cell carcinoma.

He was found to have a thick-walled cavity in the left upper lung. Being febrile he had been treated with antibiotics but the lesion grew gradually and finally diagnosed as cancer by cytology of bronchoscopically brushed specimen. On the day of admission the cavity found filled and showed water density by CT scan (Fig. 4). Positron study showed that uptake of ^{11}C-methionine was found high in the medial part of the tumour (Fig. 5). Density corrected image shows high MET deposit in the medial part of the tumour and the lateral part (probably necrotic) is sirent in MET utilization. Fig. 6 shows sequential images of tissue density corrected ^{11}C-MET after injection (not corrected for blood volume). In the first few minutes, corrected for blood volume). In the first few minutes, count is found mainly in the lung and heart and tumour remains as a relatively cold nodule reflecting blood volume difference in the tissues. But after blood isotope is cleared 15 minutes after injection the difference becomes less obvious. The tumor lung ratio in DAR(30) is 1.3.

case 3

S.O. Lung cancer, squamous cell carcinoma.

62 y.o. male. He was found to have a large mediastinal mass surrounding the right main bronchus (Fig. 7). MET uptake is found mainly in the tumour but less apparent in the density corrected image (Fig. 8). DAR(30) is 1.69, 1.58 for lung and tumour respectively.

case 4

T.S. 56 y.o. male. He was tumour in the right S3 which attached in the mediastinum. Though the tumour is apparent in the MET image clearly, it disappeared after density correction (Fig. 9, 10). DAR(30) of tumour is 1.2 tumour lung ratio is 0.6.

Results

The tissue density, extra-vascular density, blood volume, true methionine uptake and MET uptake/weight of the lung, tumor and muscle are summarized in Table 1. Mean values of tissue density of 0.27 and 0.94 and mean blood volume(%) is 0.11 and 0.21 for the lung and tumors respectively. Time course of ^{11}C count after injection of ^{11}C-methionine is shown in the Fig. 11. Whereas lung MET curve has initial clearance phase, count of tumor and muscle is almost constant up to 40 minutes.

Metabolized ^{11}C-CO_2 is counted in one MET study but not detected up to 50 minutes after MET injection.

Discussion

C-11 methionine has been reported to accumulate in the pancreas[7,8] and brain tumours[9] probably reflecting increased amino acid metabolism in the tissue. We reported already increased glucose metabolism in experimental animal tumour tissue and suggested possibilities of qualitative tumour diagnosis in the abdomen.[10] The present report suggested increased metabolic rate in protein synthesis in lung cancers as its uptake is three times more than that of the muscle. Therefore it may be referred that tumour needs much amino acid and glucose for the self-replication as well as energy sources. Whether level of metabolism differs between tumour and inflammation, and among tumours of different differentiation level, further studies still need. For this purpose lung cancers are suitable for analysis because of their high incidence and various histological types and differentiation.

But since lung is a spetial organ in the sence that it contains much amount of air and blood, apparent isotope count is always affected by them. Therefore tissue density correction is essential. We observed density and blood volume corrected lung count of C-11 methionine is higher than blood level (Fig. 11), so it may be referred that methionine is incorporated into lung and fixed there. C-11 CO_2 in alveoli should increases lung count but present data do not support it.

Another advantage of density correction is that it may also correct the count recovery of small sized tumours.[11] Full recovery of count of ECAT is only possible for the objects larger than twice of the system resolution[12] (FWHM of ECAT is 14mm). As the point spread function is nearly identical between for the emission and transmission scan, division of the former by the latter may cansel out the size-effect on the emission count. But viability of tumour tissue differs point by point as shown in case 2 and contamination of necrotic tissue is inevitable in tumours detected with positron tomography. Therefore true methionine uptake in viable tumour tissue may be higher than obtained.

Acknowledgement

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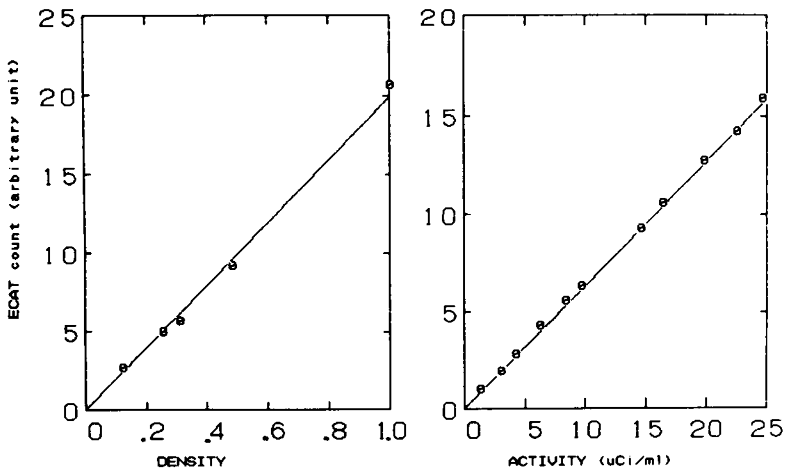

Fig. 1. Count response of ECAT in transmission and emission mode. Density of sponges of various water content is measured by transmission scan (left) and activities of C-11 is followed to decay by emission scan (right). The system measures tissue density and isotope concentration linearly.

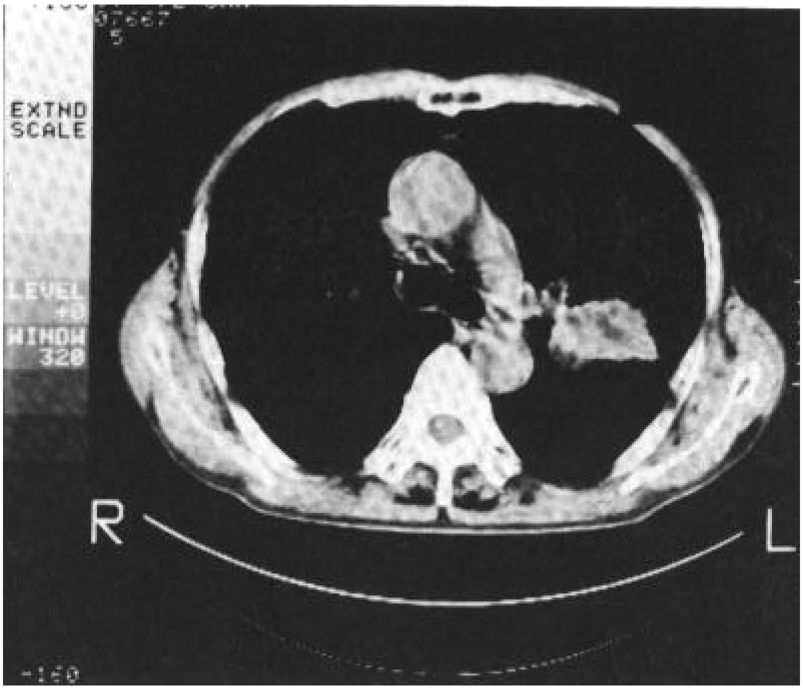

Fig. 2. X-CT image of case 1.
Squamous cell carcinoma in the right helium.

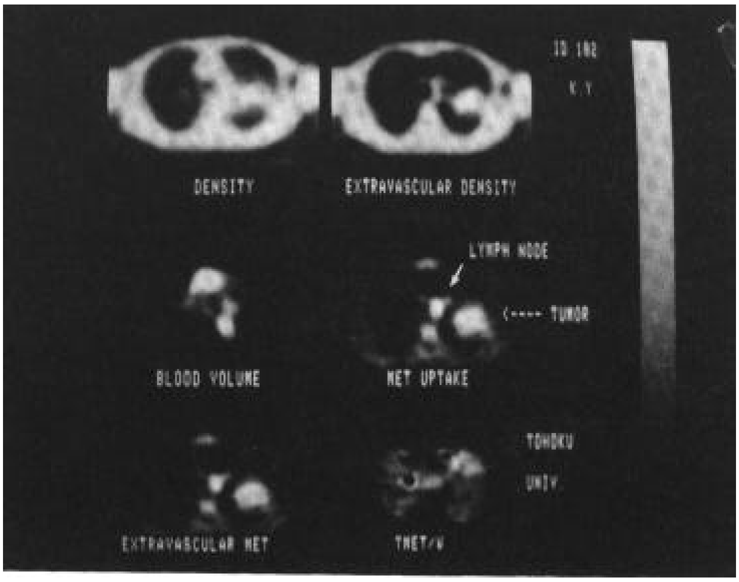

Fig. 3. ECAT image of case 1.
Apparant high uptake of C-11 methionine in the tumor (left bottom) is obscured after density correction (right bottom).
TMET/W: True methionine uptake/weight.

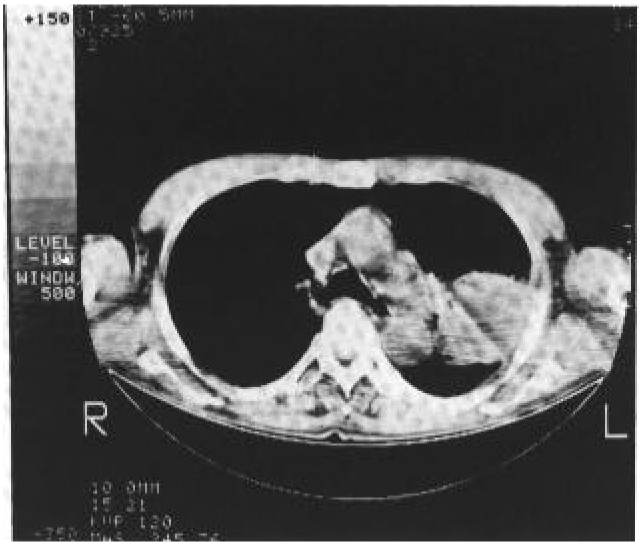

Fig. 4. X-CT image of case 2.
Squamous cell carcinoma in the left S_{1+2}.

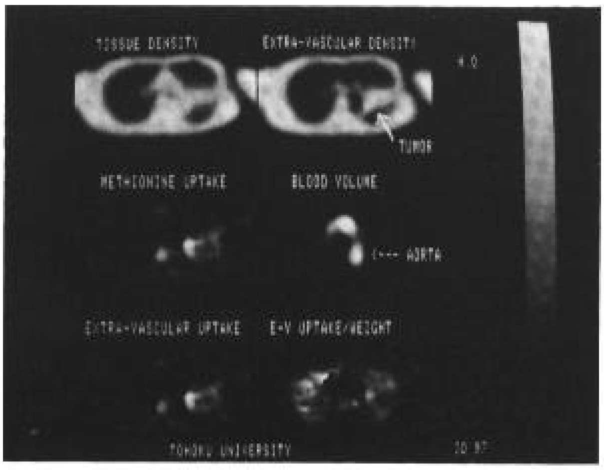

Fig. 5. ECAT image of case 2.
C-11 methionine accumulate only medial part of the tumor. Density corrected Differential Absorption Ratio of methionine at 30 minutes after injection is 2.2 and 1.6 for the tumor and the lung respectively.

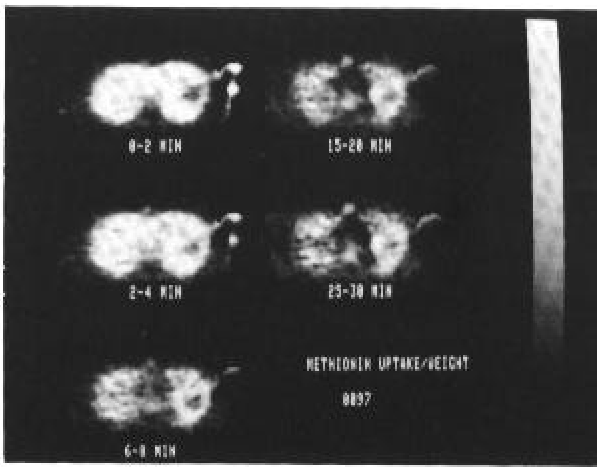

Fig. 6. Sequential images of density corrected MET uptake of the lung. Since main part of the tumor is hypovascular (BV=0.01), it is seen as a cold nodule.

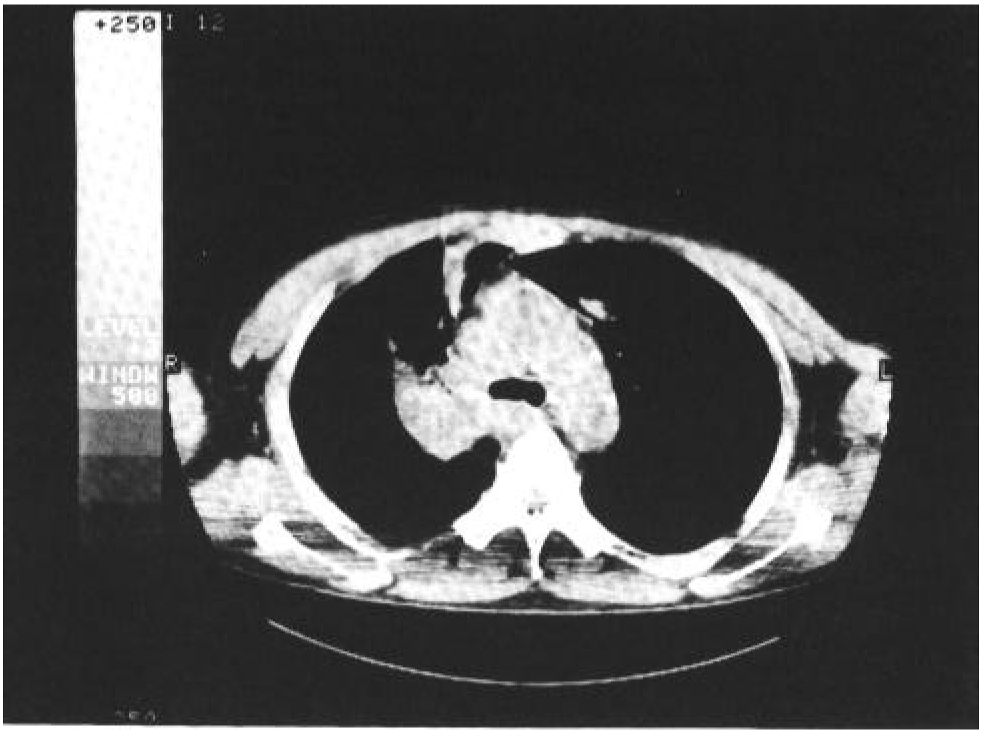

Fig. 7. X-CT image of case 3.
Squamous cell carcinoma and mediastinal lymph node involvement.

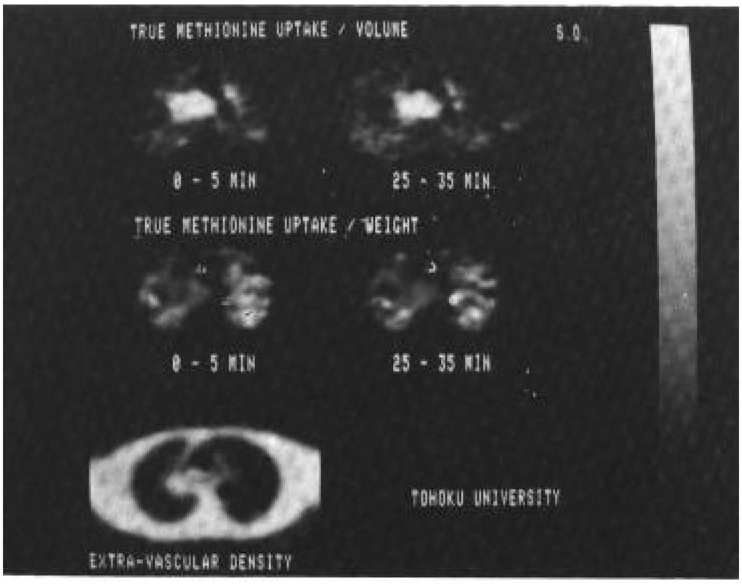

Fig. 8. ECAT images of case 3.
C-11 methionine accumulate in the tumor and lymph nodes but the contrast is lost after blood volume and density correction (TMET/W).

Fig. 9. X=CT image of case 4.
Squamous cell carcinoma in the right S_3.

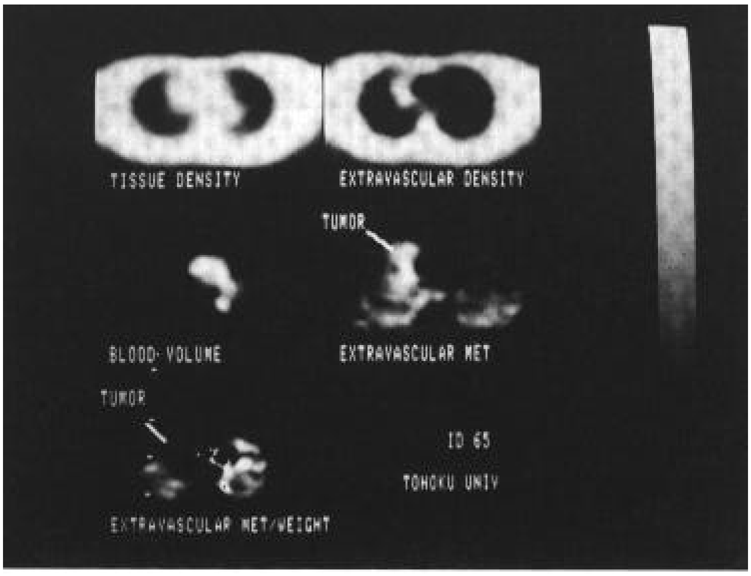

Fig. 10. ECAT image of case 4.
Density corrected extravascular uptake image shows relatively low C-11 methionine deposit in the tumor compared to the lung (low column).

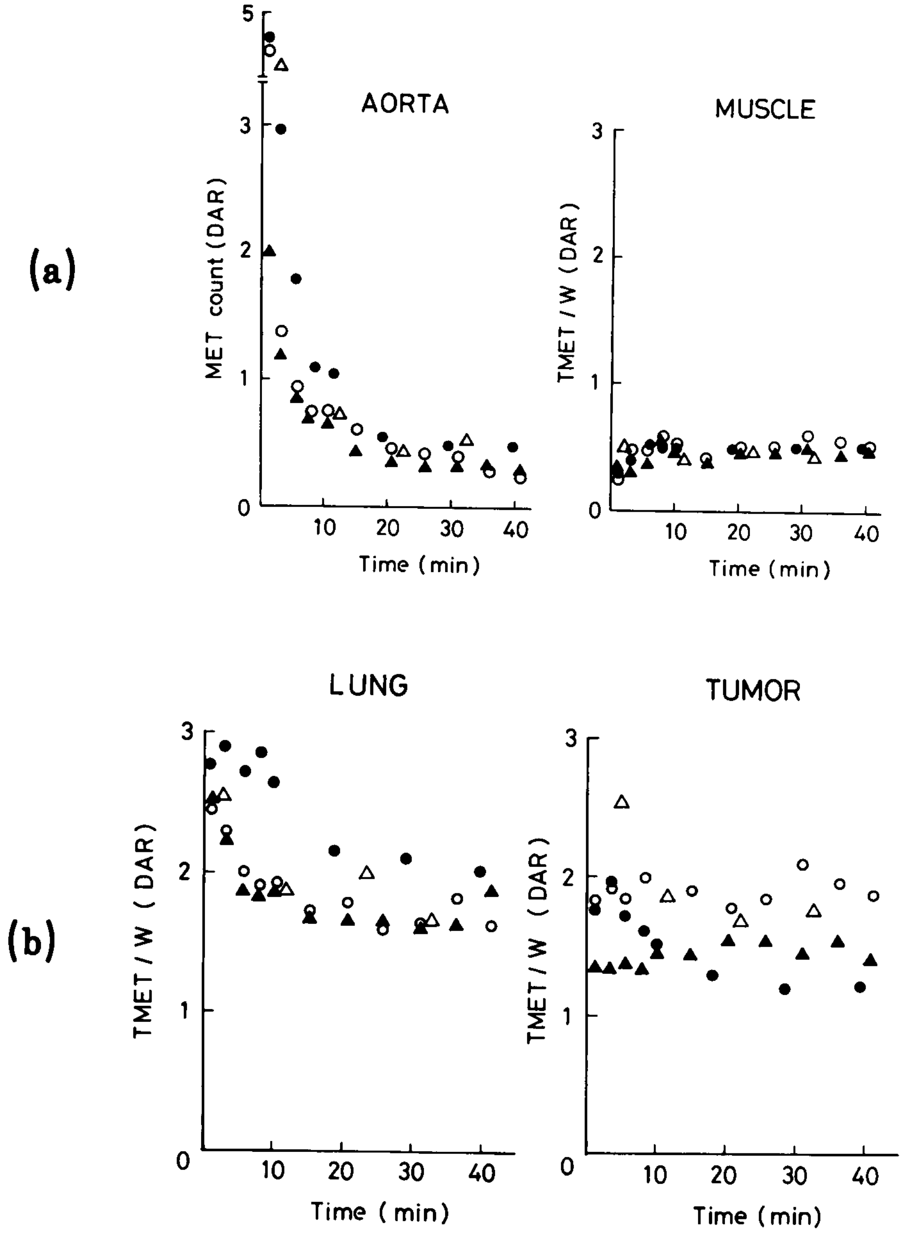

Fig. 11. Time activity curve of TMET/W (blood volume and density corrected) in the lung, tumor and muscle expressed by DAR. Aorta count is original(not corrected) DAR.
▲---▲ case 1, o---o case 2, Δ---Δ case 3, ●---● case 4.