



Original Article

Limited benefit of CT scans in tuberculosis contact tracing[☆]Takashi Yoshiyama^{a,*}, Atsuko Kurosaki^b, Hideo Ogata^c, Yuka Sasaki^d, Masao Okumura^d^a Research Institute of Tuberculosis, Japan^b Department of Diagnostic Radiology, Fukuji Hospital, Japan^c Fukuji Hospital, Japan^d Respiratory Diseases Center, Fukuji Hospital, Japan

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ABSTRACT

Objective: The detection of abnormal findings on computed tomography (CT) scans of tuberculosis contacts combined with normal plain radiographs contributes to the early detection of tuberculosis. However, the benefit of the early detection of abnormalities for the prevention of active tuberculosis during follow-up requires evaluation.

Method: We conducted retrospective comparison of the existence of CT scans of tuberculosis contacts without findings of active tuberculosis on plain radiographs at a hospital in Japan. Results: Among 243 contacts without CT scans, five developed tuberculosis during follow-up. Among 229 contacts with CT scans, 24 were judged as targets of multi-drug therapy since their CT findings were suggestive of active tuberculosis at the time of the CT screening. Among 205 contacts judged as having latent tuberculous infection with CT screening, three developed tuberculosis diseases during follow-up. Conclusion: CT scans detected abnormal findings among contacts without abnormalities of plain radiographs but there were some contacts that developed tuberculosis diseases among those with contact investigation including CT scan. The value of CT is equivocal considering the balance of true treatment, overtreatment and harm of radiation.

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1. Introduction

Computed tomography (CT) has been recognized as a tool for the detection of minimal changes of lung diseases and has been used to detect tuberculosis diseases at the time of contact investigation [1–8], especially among contacts of patients with multi-drug-resistant (MDR) tuberculosis [9], together with biomarkers [10,11]. Another way of viewing this is that many of the abnormalities that are detected with CT scans are minimal and those with findings are the targets of the treatment of latent tuberculous infection, not active diseases [12]. The prevention and treatment committee of Japan Tuberculosis Society recommends the use of CT scans to investigate contacts with normal plain chest radiographs only if contacts are with high risk of active tuberculosis at the time of investigation [13]. To date, no study has analyzed the follow-up

of contacts screened with CT; thus, the current study aimed to report the impact of CT scan for the future development of tuberculosis diseases by the comparison of contacts who did or did not undergo CT scanning.

2. Patients and method

This was a retrospective review of medical records of contacts who were referred from public health centers for the treatment of latent tuberculous infection at Fukuji Hospital, a general hospital with special clinic on tuberculosis, from 2008 to 2016 without visible abnormalities on plain chest radiographs. In Japan, household contacts, colleagues at the workplace, hospital contacts, and other close contacts are screened at public health centers with clinical signs and symptoms, interferon-gamma release assay (IGRA), and chest radiographs. If many contacts have diseases or test positive on an IGRA, the contact investigation is extended to less close contacts at the public health centers. Those who are judged as infected with tuberculosis on the IGRA test with positive or borderline results are referred to specialist clinics including

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Fukujuji Hospital where around 50 contacts are referred from public health centers every year for the treatment of latent tuberculous infection. In Japan, contacts with 0.1–0.35 IU/ml with QuantiFERON-G or QuantiFERON-GIT were judged as borderline. When the contacts are referred to Fukujuji Hospital, clinical doctors evaluate the contacts' clinical signs and symptoms, IGRA results, and chest radiograph findings and then decide whether CT scans are needed, although CT scans are not included in the recommendations on contact investigations of tuberculosis by the public health officials. The Japan Tuberculosis Society recommends the use of CT scans for limited contacts such as symptomatic persons and contacts of patients with highly infectious disease [10]. However, in Fukujuji hospital, some doctors preferred to take CT scan and some did not and the difference of doctor was the main reason of executing CT scan or not. Attending physicians judged whether each contact is with diseases or not with the information including findings of CT scan by radiologists if CT scan was taken. In Fukujuji hospital, conventional thin slice CT scan with 1 mm thickness was used for the detection of lung abnormalities. The contacts without diseases were treated with isoniazid (INH) for 6 months if the source case was deemed susceptible to INH, treated with rifampicin (RIF) for four months if the source case was resistant to INH and susceptible to RIF, and were followed up without treatment if the source case was MDR. In Japan, all tuberculosis cases were investigated with drug susceptibility testing and all contacts were treated with latent tuberculosis infection following the drug susceptibility testing of index cases. The contacts were actively followed-up at public health centers every 6 months for 2 years and passively until 2017 we calculated the proportion of clinical breakdown to tuberculosis diseases.

With this study, one radiologist and two pneumologist rechecked the CT scan findings together with the information of clinical course and bacteriological status in order to reevaluate the validity of CT scan reading at the contact investigation.

The other independent factors were sex, age, sputum smear of index cases, X ray findings of index cases, place of contact, used drugs and status of completion of treatment of latent tuberculosis infection.

The comparison of the proportion between the two groups was performed using Fisher's exact test for those when the smallest cell was 0 or 1 and the chi square test with Yates correction for continuity with a 95% significance level.

Because the study is a retrospective review of medical record, informed consent was not obtained. Privacy rights of human subjects was observed. The study was accepted by the institutional review board of research institute of tuberculosis (RIT/IRB 29-23).

3. Results

During the study period, 472 contacts (230 men, 242 women) were investigated. The median age was 45 and 99 contacts were ≥ 60 years as in Table 1. Four of them were contacts of patients with MDR tuberculosis. A flow chart of this study is shown in Fig. 1.

Among the 472 contacts, 243 contacts were not screened with CT as in Table 2. There was no difference of age, sex, sputum smear grading of index cases, and X ray findings of index cases between the CT group and non CT group. The number of subjects that became tuberculosis diseases during follow up are shown on Table 1. The risk factors of becoming tuberculosis diseases was young age at 15–19 years old and male sex. There was no significant difference of the proportion of tuberculosis diseases during follow up by IGRA status (positive or borderline), X ray findings and sputum smear status of index cases, by the mode of contact, by the execution of CT scan (5/243 without CT scan vs 3/205 with CT scan) and all eight contacts that developed tuberculosis diseases were treated with isoniazid and seven (88%) of these were completers. Four and five of these eight cases were sputum smear and culture positive respectively and one case acquired resistance to INH; that is, his source case was susceptible to INH and he was INH

Table 1
Background information of contact persons.

Factors	all(a)	Prop.	clinical TB during follow up(b)	b/a	p value
all	472		8	1.7%	0
male	230	49%	7	3.0%	0.029
female	242	51%	1	0.4%	ref.
age					
10s	22	5%	3	13.6%	0.005
20s	60	13%	1	1.7%	0.8
30s–50s	297	63%	4	1.3%	ref
60s–80s	99	21%	0	0.0%	0.32
IGRA borderline	21	4%	1	4.8%	ref
IGRA positive	330	70%	7	2.1%	0.92
IGRA unknown	121	26%	0	0.0%	
index case cavitory	162	34%	5	3.1%	0.91
index case non cavitory	145	31%	3	2.1%	ref.
index case sputum smear 3+	121	26%	3	2.5%	0.32
index case sputum smear 2+	92	19%	2	2.2%	0.39
index case sputum smear 1+	49	10%	3	6.1%	0.11
index case sputum smear \pm and negative	56	12%	0	0%	ref
contact					
household	98	21%	3	3.1%	ref
workplace	129	27%	2	1.6%	0.72
hospital	69	15%	2	2.9%	0.74
nursing facility	28	6%	0	0.0%	0.77
family at other house	22	5%	1	4.5%	0.85
others	42	9%	0	0.0%	0.62
Status of completion of latent tuberculosis treatment group					
completion	405	86%	8	2.0%	ref
died	2	0%	0	0.0%	0.96
defaulters	22	5%	0	0.0%	0.65
interruption	14	3%	0	0.0%	0.76

Prop.; proportion, CT: computed tomography, TB; tuberculosis, Dr; doctor.

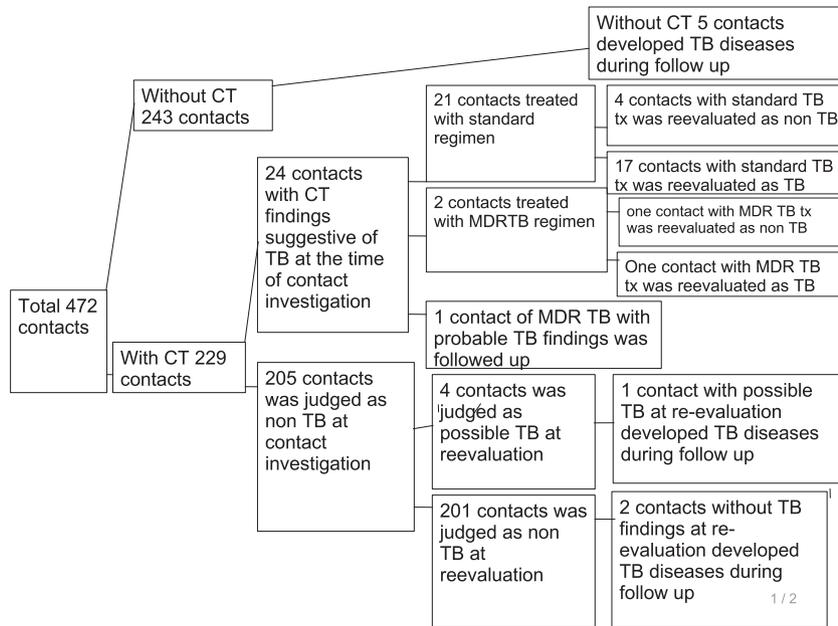


Fig. 1. Study flowchart. Abbreviations; CT: computed tomography, TB: tuberculosis, tx: treatment H/R; isoniazid or Rifampin MDR; multi drug resistant.

Table 2
CT scan result.

	total	TB findings at the beginning	no TB findings at the beginning	clinical TB during follow up
all cases	472	0	472	8
without CT	243	0	243	5
with CT	229	24	205	3

CT: computed tomography, TB; tuberculosis.

resistant at the time of the clinical tuberculosis diagnosis. He was without CT scan at contact investigation and the reevaluation of X ray findings of this case revealed abnormality at the left apex. There was no significant difference of the risk of acquisition of INH resistance by the execution of CT scan (1/243 without CT scan vs 0/205 with CT scan). The contacts that developed tuberculosis diseases during follow-up are shown in Table 3.

Among the 243 contacts without CT scan, 231 started treatment with INH and 12 contacts were treated with RIF. Among these 231 contacts, the regimens of eight were changed to RIF because of adverse drug reactions. Among the 243 contacts without CT, 219 completed treatment. During the follow-up period, five of the 243 contacts without CT developed active tuberculosis.

A total of 229 contacts were screened with CT. Four contacts were exposed to MDR tuberculosis. Among the 229 contacts with CT, 119 including one exposed to MDR tuberculosis were judged as having no findings. Among the remaining 110 contacts with findings, 24 (10.5% of 229 contacts) were judged as having suggestive active tuberculosis on the CT scan at the time of the contact investigation including three contacts of MDR tuberculosis. After a rigorous bacteriological investigation, 23 started tuberculosis treatment. One remaining contact was judged as probably having active tuberculosis, but since the index case had MDR tuberculosis, the contact was followed up for the detection of deterioration of CT findings but terminated the follow up at Fukujiji Hospital 3 months

later without deterioration due to transferring out. Among these 24 contacts that were judged as having findings suggestive of active tuberculosis, seven including one contact of MDR tuberculosis tested culture positive (four contacts with sputum, two with gastric aspirate, and one with specimen by fiberbronchoscopy). The risk factor of these 24 contacts was the family contacts including the same household and other household and age, sex, sputum smear and X ray findings of index cases were not the risk factors. The contacts that were diagnosed as having active tuberculosis at the time of contact investigation are shown in Table 4. Among 23 cases treated as tuberculosis diseases, 8 persons changed regimen due to adverse drug reaction and all 23 cases completed treatment without relapse. Among the remaining 205 (229–24) contacts who underwent CT scans and were judged as having latent tuberculosis infection (119 without findings, 86 with findings not suggestive of active tuberculosis), 199 were treated with INH and 5 were treated with RIF; one contact was followed up without treatment because she was the contact of MDR tuberculosis. Among the 204 contacts treated with INH or RIF, seven were changed from INH to RIF due to adverse drug reactions and this proportion of change of regimen was lower than those that were treated as diseases. Among these 205 contacts, 186 completed treatment for latent tuberculosis infection. During follow-up, three contacts developed active tuberculosis among these 205 contacts as in Table 3; Table 5 reveals the result of re-evaluation of CT scan findings. Among 24 contacts that were judged as tuberculosis diseases at contact investigation, the re-evaluation revealed that 19 of these were appropriately treated as probably active tuberculosis and remaining five were judged as probably not active tuberculosis cases. The re-evaluation of the CT findings of 205 contacts that were judged as latent tuberculosis infection revealed that 201 were appropriately judged as having a latent tuberculosis infection, including two cases that developed tuberculosis diseases during follow-up (Table 3), and four contacts who had been judged as latent tuberculosis infection at the time of the contact investigation were judged as possibly active tuberculosis at reevaluation including one that developed tuberculosis diseases during follow up (Table 3).

Table 3
Contacts that developed tuberculosis diseases during follow up period.

SN	Sex	Age	Contact	Computed tomography		Source		Compliance	TLTBI to diseases duration	Diseases at follow up			
				at time of contact investigation	re-eval	H suscep	Smear X ray			sm	P/Ep	cultureH	suscept
1	M	19	household	ND		suscept 2+	cavitary	defaulted	1574 days	pos	pul	pos	suscept.
2	M	54	workplace	ND		suscept 1+	non cav	complete	211 days	pos	pul	pos	resistant
3	M	26	family (not same house)	ND		suscept 3+	cavitary	complete	393 days	neg	pul	neg	unknown
4	M	46	psychiatric Hospital	ND		suscept 2+	cavitary	complete	1163 days	neg	pul	neg	unknown
5	M	37	psychiatric Hospital	ND		suscept 3+	cavitary	complete	1132 days	neg	pul	pos(BF)	suscept
6	F	18	household	Ground Grass Opacity	no TB	suscept 1+	non cav	complete	255 days	pos	pul	pos	suscept.
7	M	43	workplace	5 mm nodule c calcification	possible	suscept 3+	cavitary	complete	450 days		LN	neg.	unknown
8	M	16	household	no findings	no TB	suscept 1+	non cav	complete	846 days	pos	pul	pos	suscept.

SN: serial number, re-eval: re evaluation of computed tomography findings. TLTBI: treatment of latent tuberculosis infection duration; duration from completion of TLTBI to clinical breakdown to tuberculosis. sm. Sputum smear. P/EP; pulmonary or extrapulmonary, H suscep; isoniazid susceptibility test result.

M; male, F; female, ND: not done, pos; positive, sneg; negative, pul.: pulmonary, LN; lymph node: BF: fiberbronchoscopy. Suscept; susceptible; c; with. non cav: not cavitary.

Table 4
Contacts that were judged as active tuberculosis at the time of contact investigation by CT findings.

SN	sex	age	source		contact	Computed tomography findings	bacteriology		
			Smear	X ray			re-eval	sm	cul (specimen)
1	M	61	unknown	unknown	workplace	centrilobular nodules with 2–5 mm diameter with in the left apex	definite	neg	pos (sputum)
2	F	40	2+	non cavitary	household	centrilobular nodules in right lower lobe	definite	neg	pos (sputum)
3	F	58	2+	cavitary	Family (not in the same house)	centrilobular nodules with 2–5 mm diameter in the upper part of left lobe	definite	neg	pos (BF)
4	F	24	3+	(MDR)cavitary	workplace	may not be tuberculosis. Thickening of sub pleural lung scar	no TB	neg	neg (sputum)
5	F	39	–	non cavitary	household	peribronchiolar infiltration in the left lingular lobe	definite	neg	pos (GA)
6	F	29	unknown	unknown	household	5 mm diameter nodule in the right apex	definite	neg	pos (sputum)
7	F	47	– (BF 3+)	non cavitary	teacher	centrilobular nodules in the rt upper part of lower lobe		probable neg	neg (sputum)
8	F	63	unknown	unknown	teacher	Ground grass opacity, multiple	no TB	neg	neg (sputum)
9	F	43	3+	non cavitary	teacher	Ground grass opacity without change after treatment	no TB	neg	neg (sputum)
10	M	35	±	non cavitary	household	centrilobular nodules c 2 mm diameter in left frontal upper lobe		Probable neg	neg (sputum)
11	F	34	3+	cavitary	household	linear scar in left upper part of lower lobe	no TB	neg	neg (sputum)
12	F	53	1+	non cavitary	social worker	middle lobe centrilobular nodules s/o NTM	no TB	neg	neg (sputum)
13	F	32	–	non cavitary	nurse (hospital)	middle lobe centrilobular nodules with improvement after TB Tx		Probable neg	neg (sputum)
14	M	23	3+	cavitary	workplace	infiltration in the left lower lobe, subpleural nodule in the right lower lobe		probable neg	neg (sputum)
15	F	35	–	non cavitary	nurse (hospital)	centrilobular nodules in the left upper lobe		probable neg	neg (sputum)
16	M	28	2+	cavitary	household	centrilobular nodule in right lower lobe and subpleural nodule		probable neg	neg (sputum)
17	M	42	3+	cavitary	workplace	centrilobular nodules on both apexes		probable neg	neg (sputum)
18	M	16	3+	(MDR)cavitary	household	centrilobular nodules in the left upper lobe		definite neg	pos (GA)
19	F	35	3+	cavitary	household	centrilobular nodules in the rt upper part of lower lobe		probable neg	neg (sputum)
20	F	55	+	non cavitary	Family (not in the same house)	centrilobular nodules in the right apex		probable neg	neg (sputum)
21	M	57	±	cavitary	workplace	centrilobular nodules in the right apex		probable neg	neg (sputum)
22	F	55	3+	cavitary	Family (not in the same house)	scar with centrilobular nodules in lt lower lobe ground glass opacity in rt lung		probable neg	neg (sputum)
23	M	26	2+	non cavitary	Family (not in the same house)	bud in tree in the lower lobe		definite neg	pos (sputum)
24	F	56	(MDR)	unknown	teacher	centrilobular nodules in the right upper lobe		probable neg	neg (sputum)

SN: serial number, TLTBI: treatment of latent tuberculosis infection M; male, F; female, sm; smear, cul; culture, pos: positive, neg: negative, BF: fiberbronchoscopy. GA(gastric aspirate). MDR multi drug resistant. BF: broncho fiberscopy, c; with, NTM; non tuberculosis mobacteria, Tx; treatment.

4. Discussion

By adding a CT scan, the number of detected tuberculosis cases increased at the time of contact tracing as reported previously

[1–7] and addition of CT scan reduced the risk of tuberculosis diseases during follow up among contacts by one retrospective analysis [8]. With our study, the proportion of clinical breakdown to tuberculosis during follow-up and the proportion of acquiring INH

Table 5

Reevaluation of CT scan findings (within the parenthesis are the number of contacts that developed tuberculosis diseases during follow up) findings at contact investigation.

		active TB	other findings	normal	
reevaluation	active TB	19	4	(1)	0
	other findings	5	82	(1)	0
	normal	0	0		119 (1)
	total	24	86	(2)	119 (1)

CT: computed tomography, TB; tuberculosis.

resistance was fewer among those with CT scan than among those without CT scan but this difference was not significant.

There are costs and benefits of addition of CT scan at contact investigation of tuberculosis. The benefit is the reduction of clinical tuberculosis cases during follow up and reduction of acquisition of INH resistance among cases, although our findings did not show the significant difference between contacts with and without CT scan. The costs include 1. Monetary cost, 2. Effect of Radiation on health [14], although the risk may be reduced by the wide usage of low dose CT screening [15] and the proportion of precision inspection after low dose CT screening may depend on the quality of radiologists, 3. Unnecessary treatment of contacts with findings that are not related to tuberculosis, 4. Unnecessary treatment of tuberculosis diseases in the early stage which can be cured without full four drug regimen but only with INH or no treatment even among culture positive persons with new infection [16].

We consider that CT scanning especially low dose CT scan, at the time of contact tracing may be useful for the detection of active tuberculosis but that a prospective comparison with a cost effectiveness analysis is necessary to verify the settings when it is useful.

The younger generation (<20 years of age) and male sex were not factors of TB diseases with CT scan at contact investigation but were factors of development to TB diseases during follow up. This difference of clinical TB as prevalence at contact investigation and as incidence during follow up need further investigation on the nature of immunological response to tuberculosis diseases among infected persons.

There were some discrepancies in the clinical decision at the time of the contact investigation and reevaluation of the CT scan. This reveals the difficulty of judging the CT scan findings of IGRA-positive contact of tuberculosis.

All four contacts of MDR tuberculosis was examined with CT and one person was without findings and 3 persons were judged as with findings suggestive of tuberculosis including one bacteriologically positive case, one that was judged as “NOT tuberculosis with re-evaluation” and one that were could not be followed up because of transfer out. The number is too small to conclude anything but careful follow up including CT scan will be necessary for the contacts of MDR tuberculosis.

There are several serious limitations of this study. This study is not prospective and cannot be free of selection bias, as the CT scan might be taken for those with a higher risk of being an active disease and a higher risk of the development of active diseases such as contacts of highly infectious cases [17], but we consider it not so likely because there was no difference of X ray findings and sputum smear positivity of index cases between CT group and non CT group. The second limitation is that the follow-up was performed by the public health center rather than the study group following the guidelines of tuberculosis control, and its quality was not verified;

some of the contacts that were diagnosed with active diseases during the follow-up period might have been treated in another hospital. However, we believe that there will be little difference in the quality of follow-up between CT group and non CT group. The third limitation is the lack of fingerprinting for the confirmation of real relationship of infection and clinical diseases.

In conclusion, our findings suggest the need for further evaluations of CT scans at the time of contact tracing.

Declaration of interest

None.

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