



MDR-TB: duration of treatment, follow-up and final outcome classification

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Outcome of MDR-TB

- Reported duration of MDR-TB treatment differed considerably
- Outcome of MDR-TB varied widely, ranging from 97% to less than 40%.
- Methods used in analyzing the outcome of MDR-TB were not standardized until recently

Treatment of 171 Patients with Pulmonary MDR-TB

- 87/143 (65%) patients have response (negative sputum culture for 3 consecutive months).
- 12/87(14%) patients with response subsequently had relapses.
⇒ The overall response rate was 56% over a mean period of 51 months.

Treatment of 171 Patients with Pulmonary MDR-TB

Exclusions from the Outcome Analysis

Of the 171 patients, 37 were excluded from the analysis of the outcome of chemotherapy for the following reasons: 8 died after receiving therapy for two months or less; 22 were lost to follow-up before they were observed long enough during chemotherapy; 3 did not meet the criterion of three months of negative sputum cultures before surgical resection, although they had had favorable responses; 1 deferred definitive therapy because of pregnancy; and 3 had had no positive cultures within the month before therapy started.

- Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. *Int J Tuberc Lung Dis* 2000;4:758-64.
 - Treatment lasts for a mean of 608 days (range 268 – 1626 (**4.5years**)).
 - 75% were considered cured.
- Treatment of Multidrug-Resistant Tuberculosis in San Francisco. *Clin Infect Dis* 2005;40:968-75
 - The median time for conversion of cultures for mycobacteria to negative was 14.6 weeks (range, 4.0– 179.3 weeks (**3.4 years**)), respectively.
 - Thirty two (97%) of the 33 HIV-seronegative patients were cured

Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis

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SUMMARY

SETTING: Globally it is estimated that 273 000 new cases of multidrug-resistant tuberculosis (MDR-TB, resistance to isoniazid and rifampicin) occurred in 2000. To address MDR-TB management in the context of the DOTS strategy, the World Health Organization and partners have been promoting an expanded treatment strategy called DOTS-Plus. However, standard definitions for MDR-TB patient registration and treatment outcomes do not exist.

OBJECTIVE: To propose a standardized set of case registration groups and treatment outcome definitions for MDR-TB and procedures for conducting cohort analyses under the DOTS-Plus strategy.

DESIGN: Using published definitions for drug-susceptible TB as a guide, a 2-year-long series of meetings, conferences, and correspondence was undertaken to review

published literature and country-specific program experience, and to develop international agreement.

RESULTS: Definitions were designed for MDR-TB patient categorization, smear and culture conversion, and treatment outcomes (cure, treatment completion, death, default, failure, transfer out). Standards for conducting outcome analyses were developed to ensure comparability between programs.

CONCLUSION: Optimal management strategies for MDR-TB have not been evaluated in controlled clinical trials. Standardized definitions and cohort analyses will facilitate assessment and comparison of program performance. These data will contribute to the evidence base to inform decision makers on approaches to MDR-TB control.

KEY WORDS: multidrug-resistant TB; definitions; treatment outcome; cohort analysis

Outcome of MDR-TB: Cure

- An MDR-TB patient who has completed treatment according to **country protocol** and has been **consistently culture-negative (with at least five results) for the final 12 months of treatment.**
- If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures, taken at least 30 days apart.

Outcome of MDR-TB: Failed

- Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive.
- Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor response or adverse events.

Int J Tuberc Lung Dis 2005;9:640-5

Outcome of MDR-TB: failed

- Currently, failed is not defined as sputum positive at XX months.
- Patients classified as failed may differ substantially in different settings,
 - In one setting, patients may be declared failed if sputum remains positive after 12-month medical treatment
 - in another setting, modification of treatment regimen may first be made, resection surgery performed and treatment extended for years till all efforts fail.



Outcome of MDR-TB: failed

- does not take modification of regimen due to positive sputum into account.
- Guidelines for the programmatic management of drug-resistant tuberculosis, WHO, 2006
 - Patients who do not show signs of improvement after four months of treatment are at risk for treatment failure
 - The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed.

MDR-TB: Case one

- treated with a standardized MDR-TB regimen,
- sputum smear and culture conversion at 2 months.
- continued treatment and was cured.
- Total treatment duration: 20 months.

MDR-TB : Case Two

- Treated with an individualized MDR-TB regimen.
- Smear converted to negative at 6th month.
- At 12th month, culture remained positive.
- Regimen modified by adding PAS and clofazimine and replacing ciprofloxacin with moxifloxacin.
- Culture conversion at 3 months after modification of regimen.
- Treatment continued 18 months after culture conversion and the patient was cured.
- Total treatment duration: 33 months.

MDR-TB : Case Three

- Treated with an individualized regimen.
- Culture conversion at 6 month but become positive again at 14 month.
- Regimen reinforced with PAS, clofazimine and PZA.
- At 20 month, sputum remained positive and resection surgery was performed to remove cavities.
- Sputum conversion was achieved after surgery.
- Treatment was continued till 18 months after sputum conversion and the patient was cured.
- Total treatment duration: 38 months.

Outcome of MDR-TB: failed

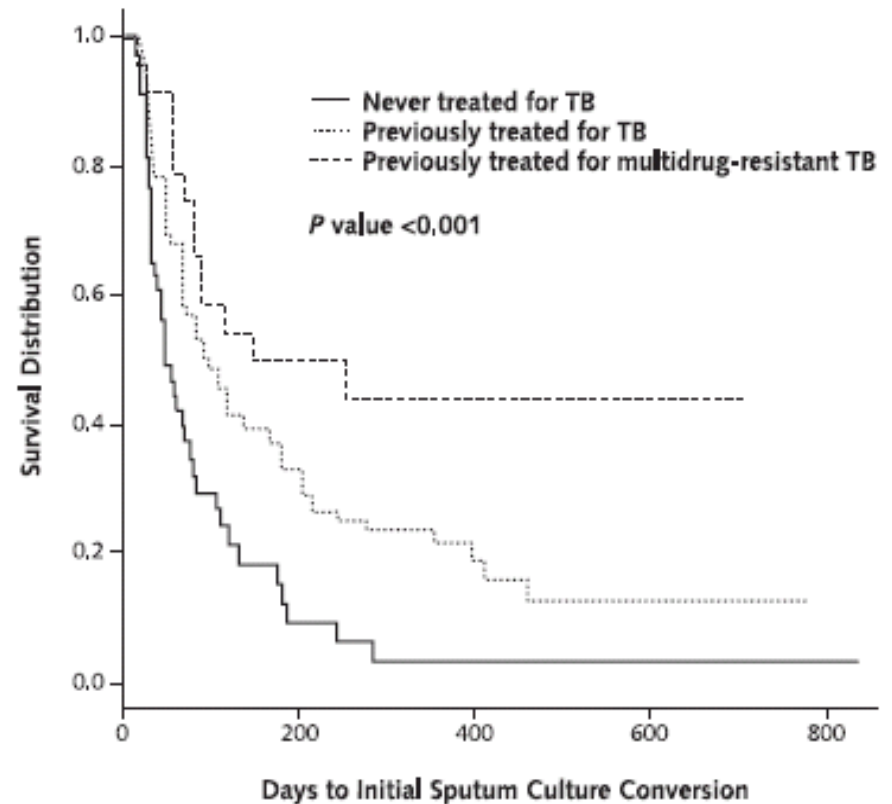
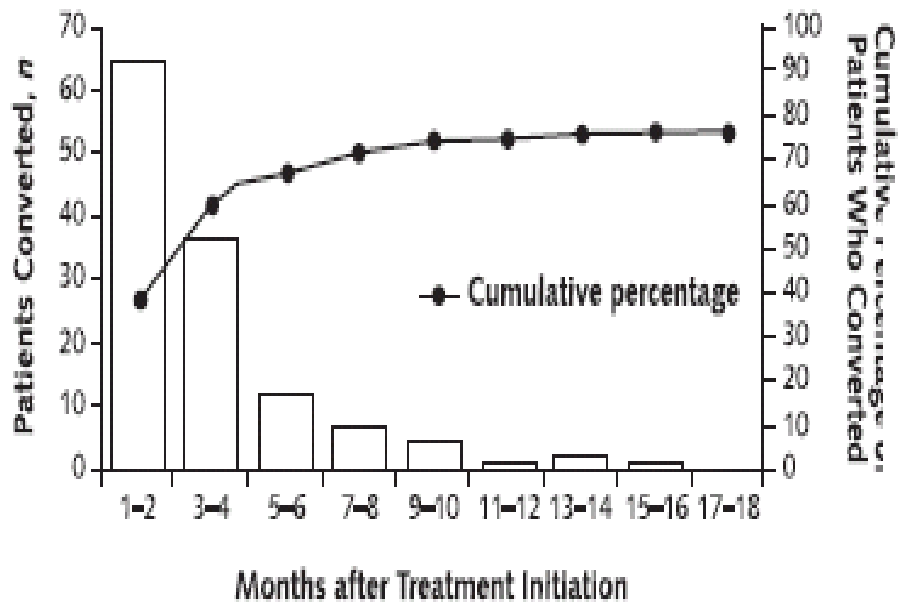
- If treatment regimen was not modified and resection surgery not performed, outcome of case 2 and case 3 would be failed.
- It is reasonable to classify case 2 and case 3 as failed, when modification of regimen is made.

Clinical outcome of individualised treatment of MDR-TB in Latvia

- Treatment continued for 12–18 months after *M tuberculosis* culture conversion,
- Treatment lasted a median of 18 months (range 1.0–37.5)

	Never treated for tuberculosis n=55	Previously treated for tuberculosis n=119	Previously treated for MDRTB n=30
Outcome			
Cure	38 (69)	76 (64)	13 (43)
Completion	4 (7)	4 (3)	0
Death	2 (4)	10 (8)	2 (7)
Failure	3 (6)	15 (13)	11 (37)
Default	8 (15)	14 (12)	4 (13)
Total	55 (100)	119 (100)	30 (100)

Time to Sputum Culture Conversion in Multidrug-Resistant Tuberculosis, Latvia



Holtz T H, Ann Intern Med 2006;144:650-9.

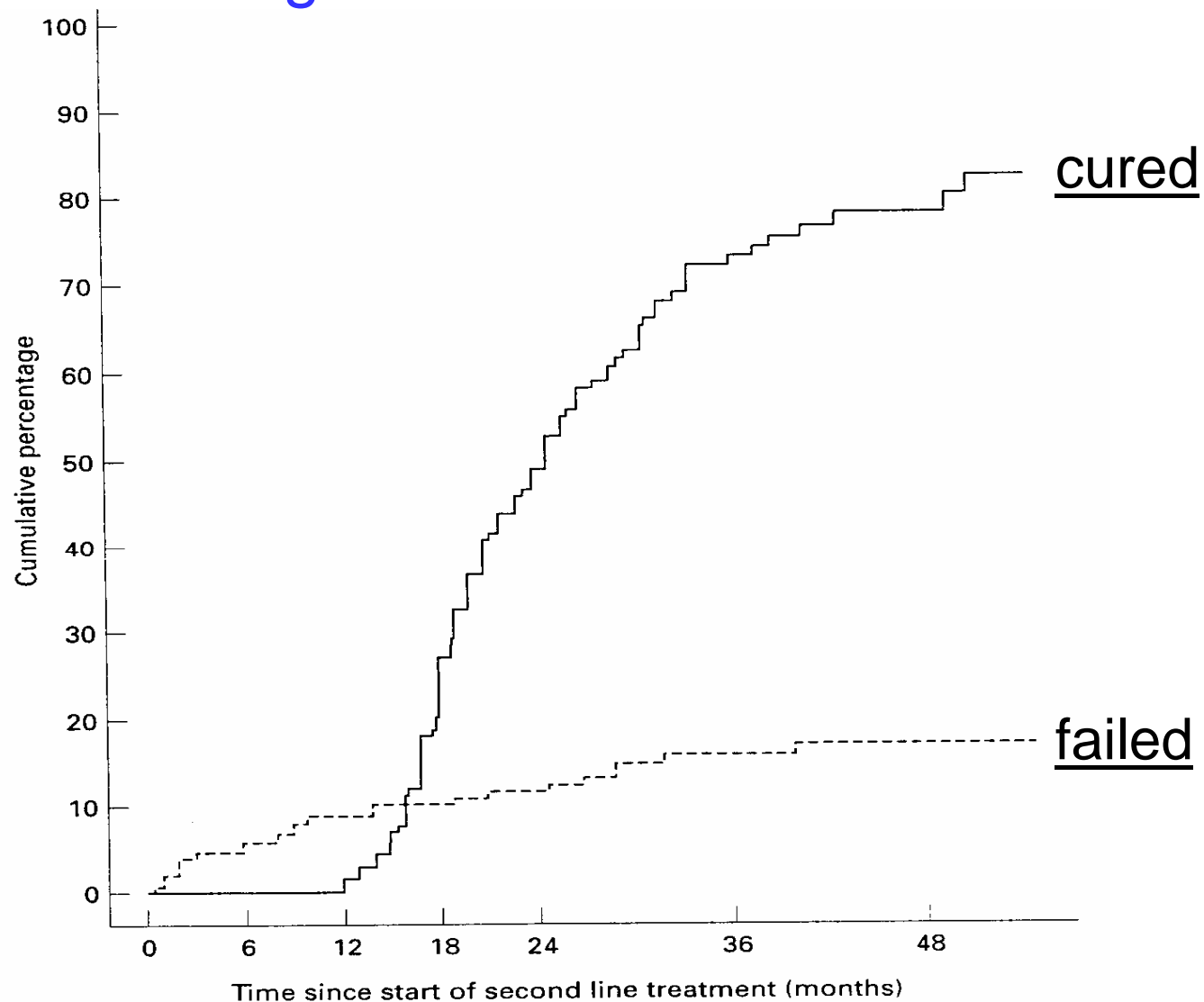
Comprehensive Treatment of Extensively Drug-Resistant Tuberculosis

- In patients without conversion of sputum culture after 4 months of treatment, drug-susceptibility testing was performed, with reinforcement of the regimen (defined as the addition or substitution of two agents that were likely to be effective), if possible. This practice was repeated as necessary.
- 29 (60.4%) XDR-TB patients completed treatment or were cured, as compared with 400 (66.3%) MDR-TB patients ($P = 0.36$).

Comprehensive Treatment of Extensively Drug-Resistant Tuberculosis

- Duration of treatment
 - Median 24.9 months
 - Interquartile range 13.3–29.0
- 7 of the 48 patients underwent resection surgery
 - No. of months from treatment initiation to surgery
 - median (interquartile range) 11.6, (7.1–24.1)
 - No. of months of treatment for patients undergoing surgery
 - median (interquartile range) 31.2 (25.1–57.9)

Outcome of second-line tuberculosis treatment in migrants from Vietnam



Pulmonary resection in the treatment of patients with pulmonary MDR-TB in Taiwan

Indication of surgery

- Group A: Medical treatment failure
 - Persistent sputum culture-positive for *M. tuberculosis* despite treatment with adequate second-line anti-TB drugs for at least 12 months.
- Group B: Prevention of treatment failure
 - Surgery in the early stages of treatment for patients whose resistance pattern and extent of lung destruction, based on our previous experience, predicted a high probability of treatment failure
- Group C: Prevention of relapse
 - Surgery in the late stages of treatment for patients with sputum conversion, yet still demonstrating a possibility of relapse that was of concern to us



Pulmonary resection in the treatment of patients with pulmonary MDR-TB in Taiwan

	Pre-operative treatment Mean and range (months)	Bacteriological Response <i>n</i> (%)
Medical treatment failure, <i>n</i> =6	20.6 (13–33)	5 (83.3)
Prevention of treatment failure, <i>n</i> =15	4.5 (2–7)	13 (92.8)
Prevention of relapse, <i>n</i> =5	14.2 (10–19)	5 (100)

Outcome of MDR-TB, Taipei 1992-1996 cohort, 6-year follow-up

- Cure: culture negative and documented to remain culture negative 1 month later, and never documented to become positive again up to 18 months after commencing treatment.
- Failure: remained positive or became positive again 12 months after commencing the course of treatment.



Outcome of MDR-TB, Taipei 1992-1996 cohort, 6-year follow-up

	No.	Success	Failed	Died	Defaulted
		(Percent)			
Total	299	52.1	10.4	9.4	29.1
First line	61	57.4	*	11.5	31.2
Second line without Fluoroquinolone	113	38.9	16.8	14.2	30.1
Second line with Fluoroquinolone	125	59.2	9.6	4.0	27.2

Chiang C-Y, et al Eur Respir J 2006; 28: 980–985

Cohort analysis

regimen failure vs patient failure

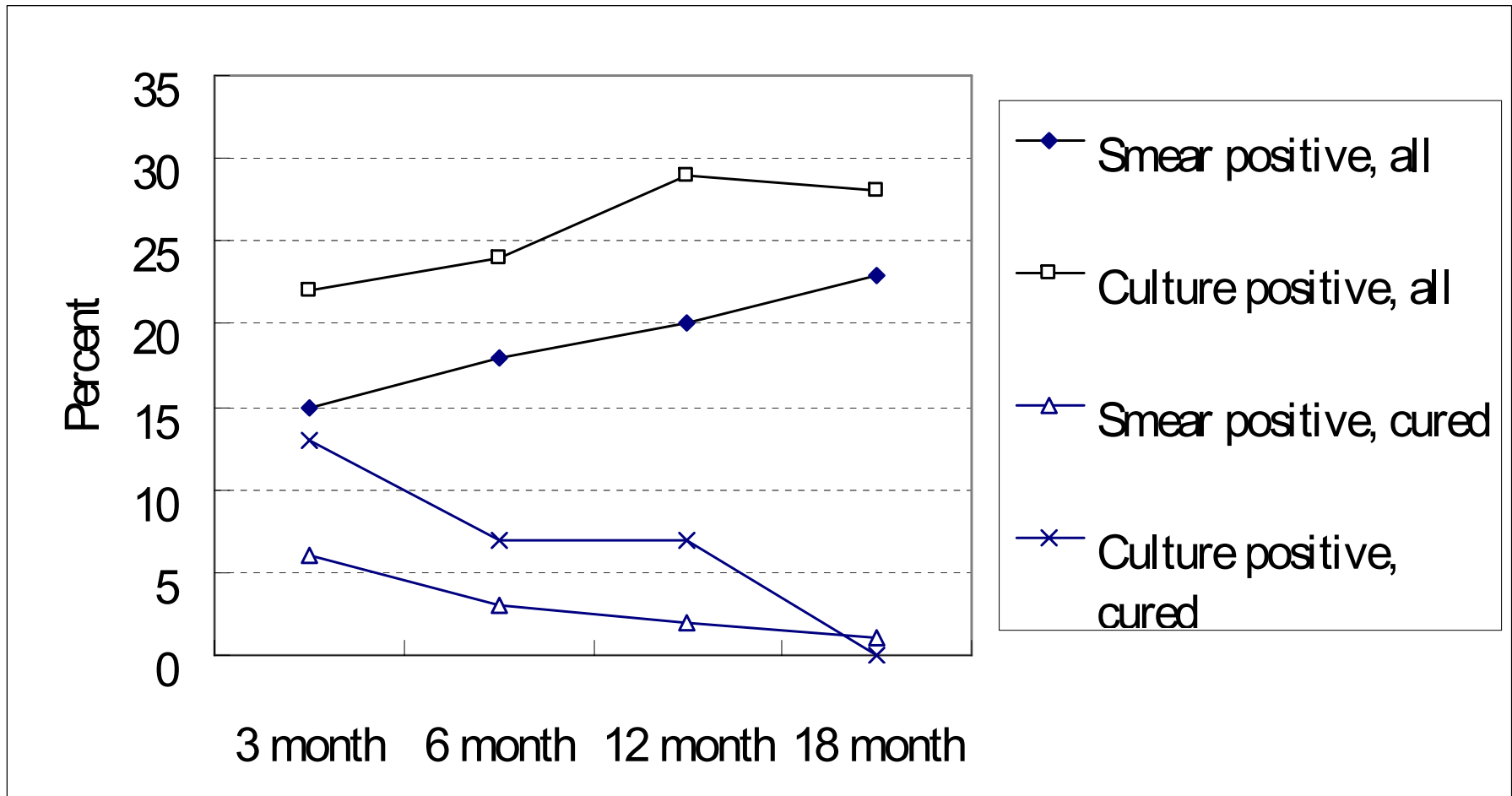
- if modification of MDR-TB regimen is made in consideration of potential failure, outcome should be failed and the patient re-registered as MDR-TB previously treated with second line drugs.
- Exactly the principle in the management of new and retreatment TB patients

The way forward

Outcome of MDR-TB: failed

- Failed defined as sputum positive at XX months: XX = 6, or 4 or 8?
- Sputum positive: smear or culture?
 - Smear positive/culture positive
 - Smear negative/culture negative
 - Smear positive/culture negative
 - Smear negative/culture positive

Standardised second-line drug treatment for chronic tuberculosis patients, Peru



- 466 patients enrolled, 87% tested had MDR-TB: 48% cured, 12% died, 28% did not respond to treatment, 11% defaulted

Suárez P G, Lancet 2002;359:1980-9.

Outcome of MDR-TB, Taipei 1992-1996 cohort, 6-year follow-up

- Among the 153 patients who were cured, full information was available to evaluate the entire bacteriological course of 139 (90.8%).
 - 115 (82.7%) had sputum culture conversion within 3 months,
 - 126 (90.6%) had sputum culture conversion within 6 months,
- Of the 29 patients who failed
 - 26 (90.0%) remained persistently positive up to 12 months.

Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh

	<i>n</i> (%)
Status at end of intensive phase (3 months), <i>n</i> = 58	
Died by 3 months	1 (2)
Defaulted by 3 months	2 (3)
Smear-negative	47 (81)
Culture-negative	51 (88)
Smear-positive	8 (14)
Culture-positive	3 (5)
Culture-contaminated	1 (2)

Regimen: 3KCOPHZE/12OPHZE/6EP
kanamycin (K), clofazimine (C), ofloxacin (O), prothionamide (P)



Alternative: sub-categories of treatment success

1. cured/failed with modification of regimen,
2. cured/failed with surgery,
3. cured/failed with both modification of regimen and surgery.

In conclusion

- Current definition of failed of MDR-TB needs to be re-considered
 - Failed could be defined as positive sputum at XX month
- Patients who need modification of MDR-TB regimen due to the consideration of inadequate regimen should be classified as failed and re-registered as retreatment cases