

Faculty disclosure

There is no financial interests or relationships with any of the commercial supporters.

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5-FU ointment for treating cholesteatoma



Haruo Takahashi, M.D.
Emeritus Professor
Nagasaki University, Japan

5-FU (5-fluorouracil)

1. It is an anti-neoplastic agent, and its local application (ointment) is effective especially for skin tumors.
2. It is also effective for premalignant proliferative lesions of the skin such as actinic keratosis (Eaglstien et al, 1970).
3. Side effect is extremely rare in case of local application.



History of 5-FU treatment of cholesteatoma

Smith MFW: *Laryngoscope* 95:1202-1203,1985.

the first report on the use of 5-FU on cholesteatoma

Sala DT: *Ear-Nose-Throat-J* 73:412-414,1994.

reconfirmed its clinical efficacy and safety

Wright CG, et al: *Am J Otolaryngol* 12:133-138,1991.

confirmed its efficacy in animal experiments

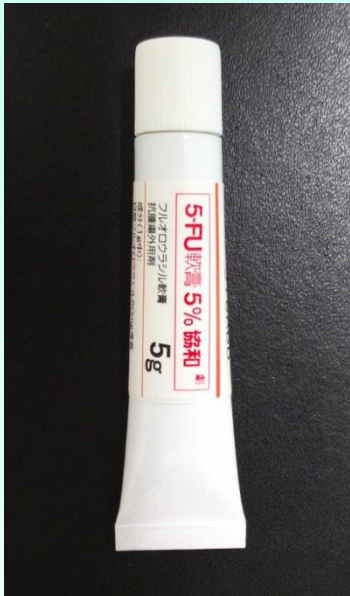
Funabiki K, et al: *Otol Jpn* 8:479,1998.

the first report from Japan

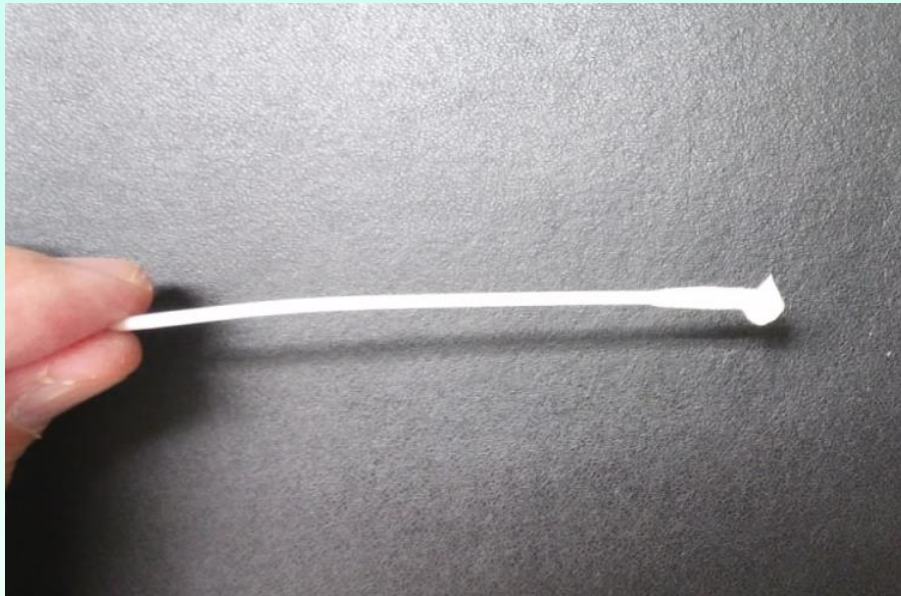
Takahashi H, et al: *ANL (Tokyo)* 32:353-357,2005.

reported on experiences in 50 cases

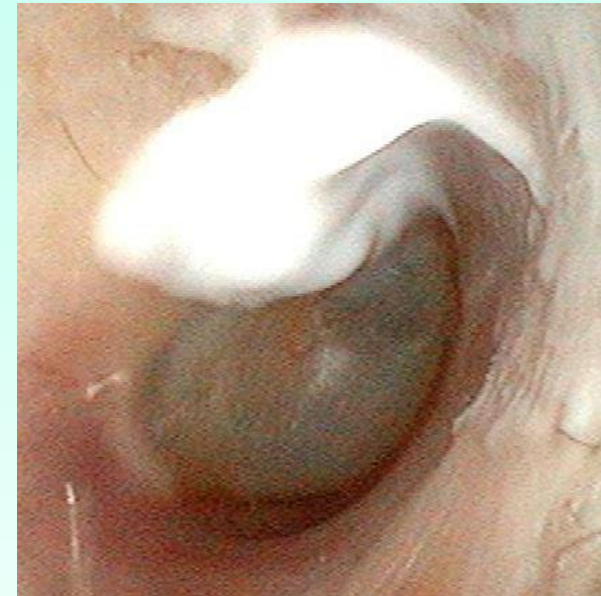
Procedure



5-FU
ointment



A volume of half of a rice grain (2-3 mm³) is used with a cotton stick



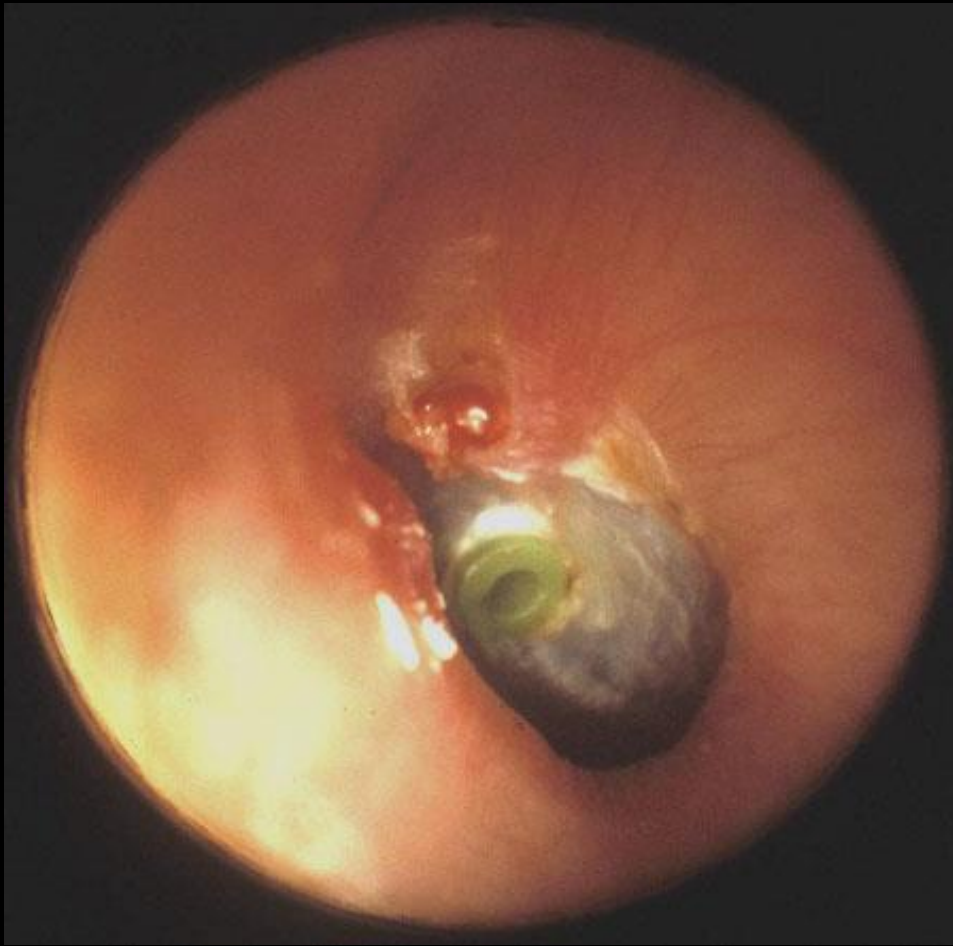
5FU ointment is
applied on the
surface

Treatment is usually given for 3 - 4 times with an interval of 1 - 3 weeks.

When necessary, ear drops containing antibiotics, steroids and/or anti-fungal agents are used.

First case I experienced

(Attic cholesteatoma, 20 y.o., man)



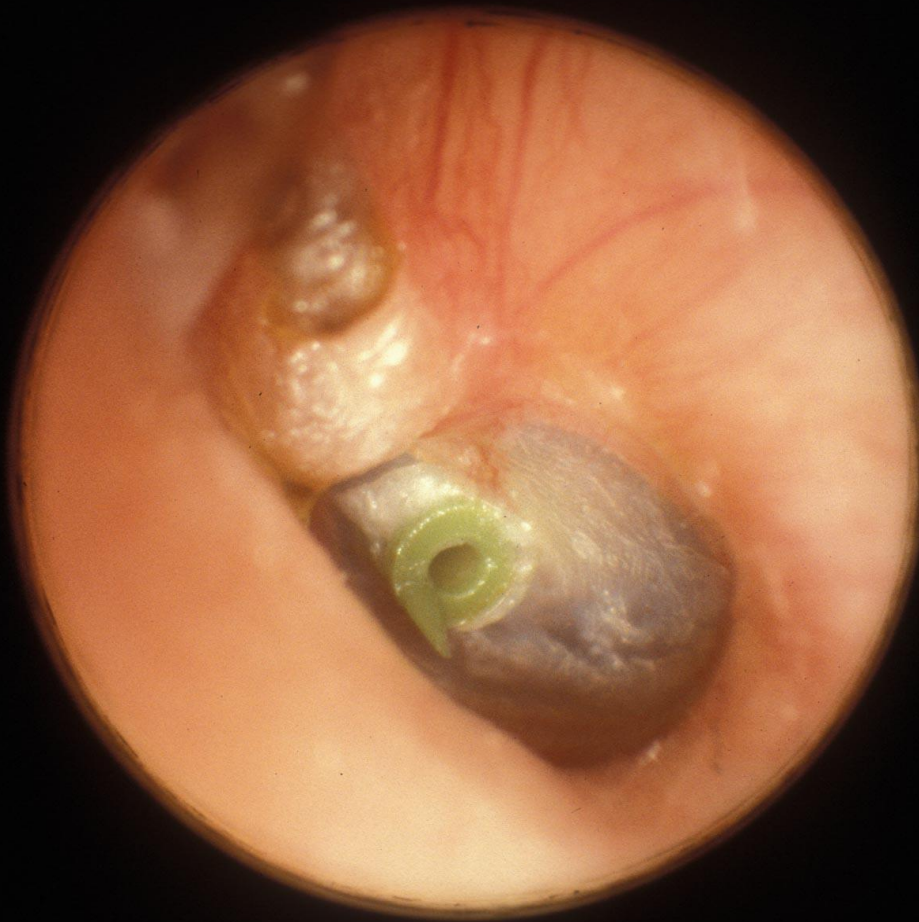
Before treatment



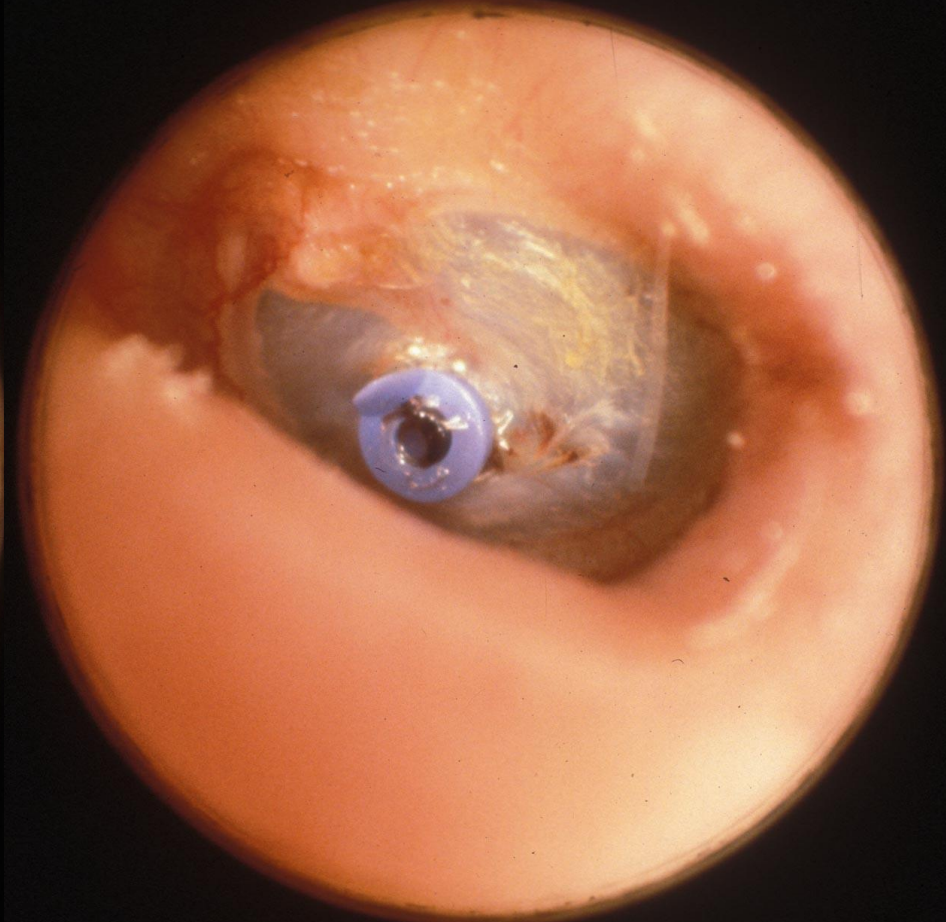
1 week after application
of 5-FU ointment

First case I experienced

(Attic cholesteatoma, 20 y.o., man)



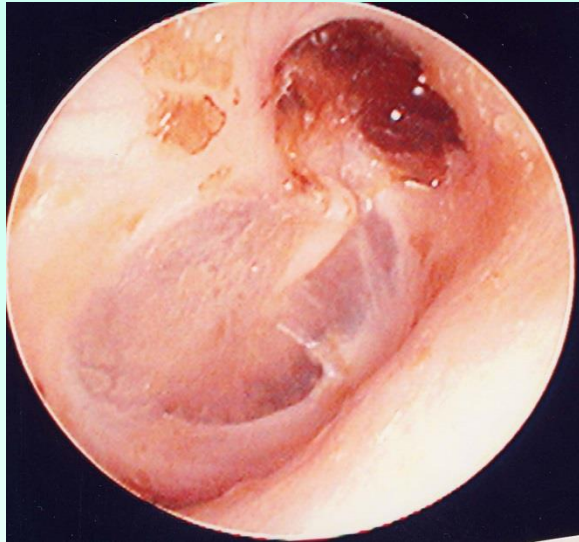
4 weeks after
treatment



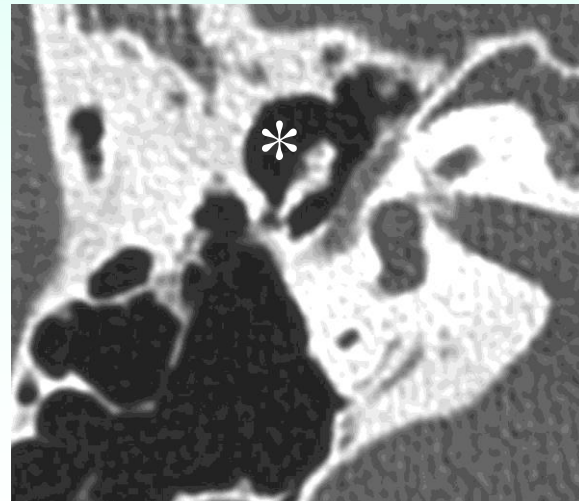
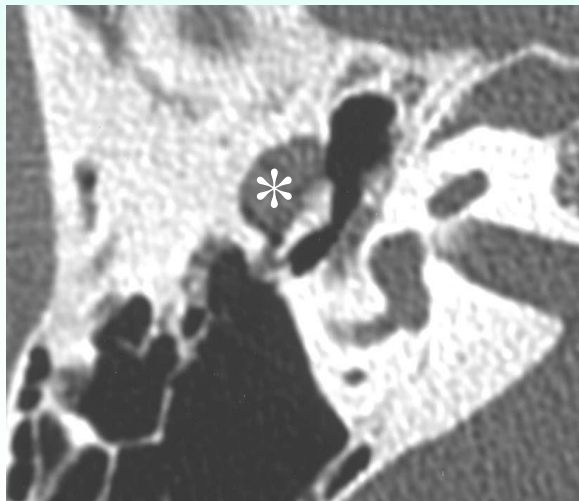
2 years after treatment

Case. Attic cholesteatoma (19 y.o., girl)

Eardrum



CT



Before treatment

After treatment

Case. Attic cholesteatoma (33 y.o., woman)

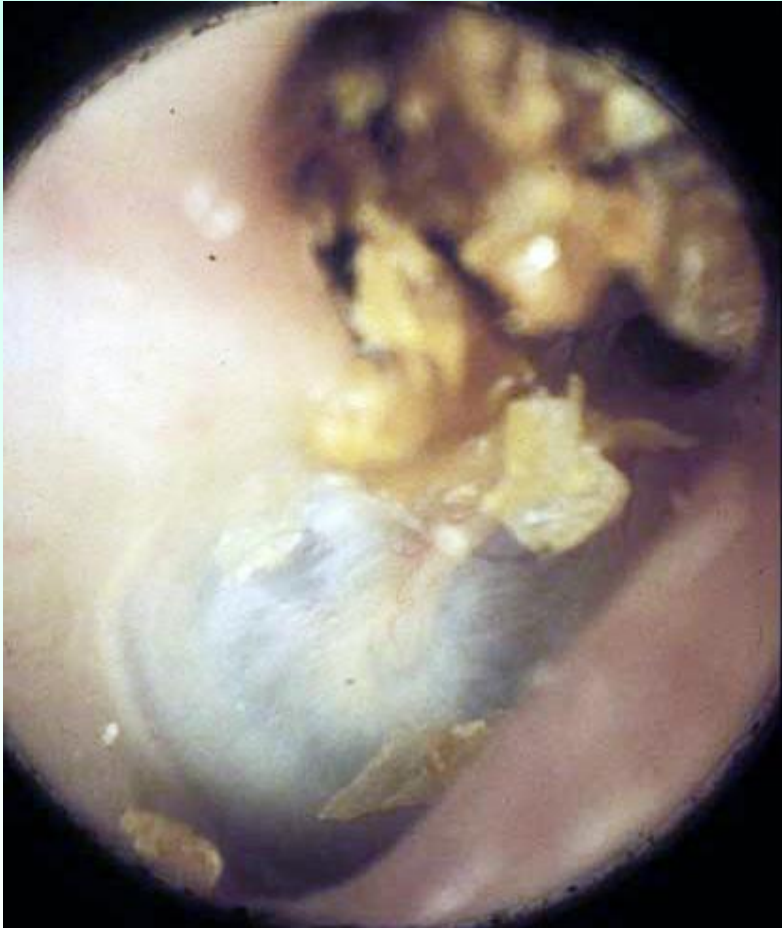


Before treatment



11 months after
treatment

Case. Attic cholesteatoma (70 y.o., man)



Before treatment



7 months after
treatment

Case. Attic cholesteatoma (73 y.o., woman)



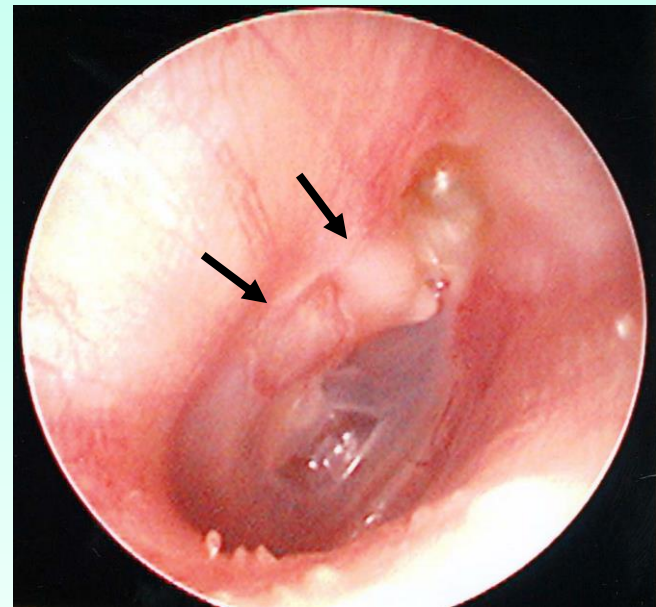
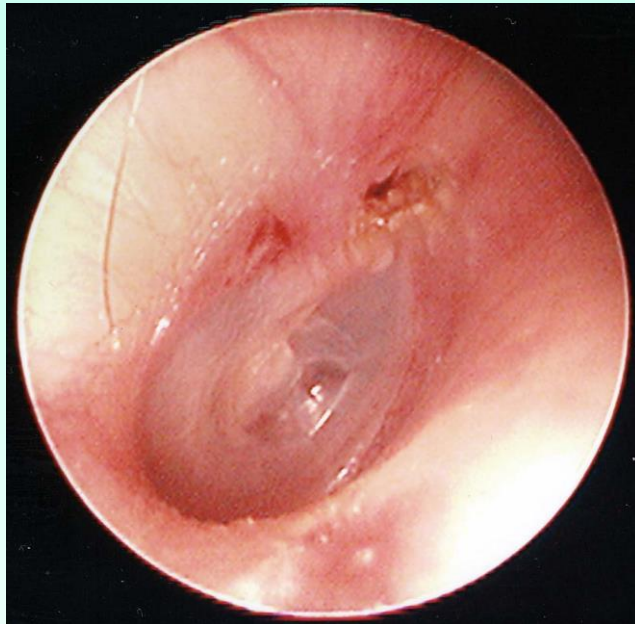
Before treatment



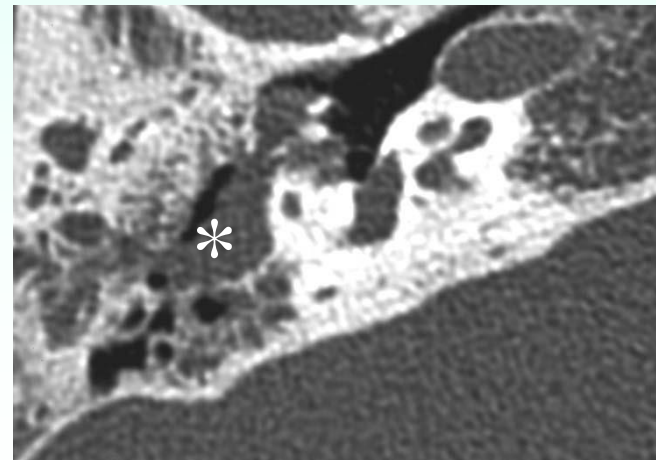
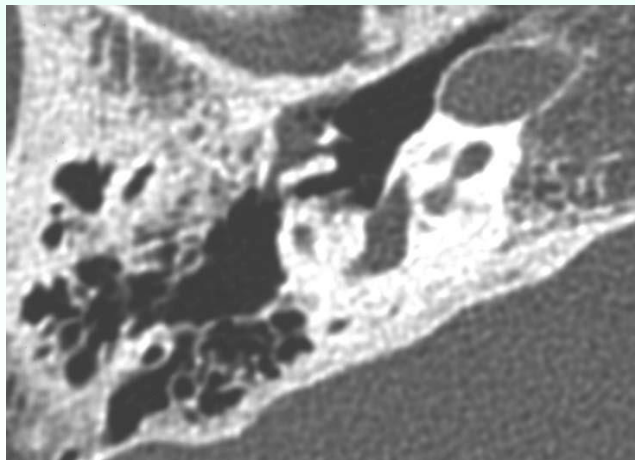
2 weeks later

Case. Attic cholesteatoma (54 y.o., man)

Eardrum



CT



Before treatment

After treatment

Subjects

Aural cholesteatoma 103 patients (105 ears)
(mean age: 53, children 2 ear)

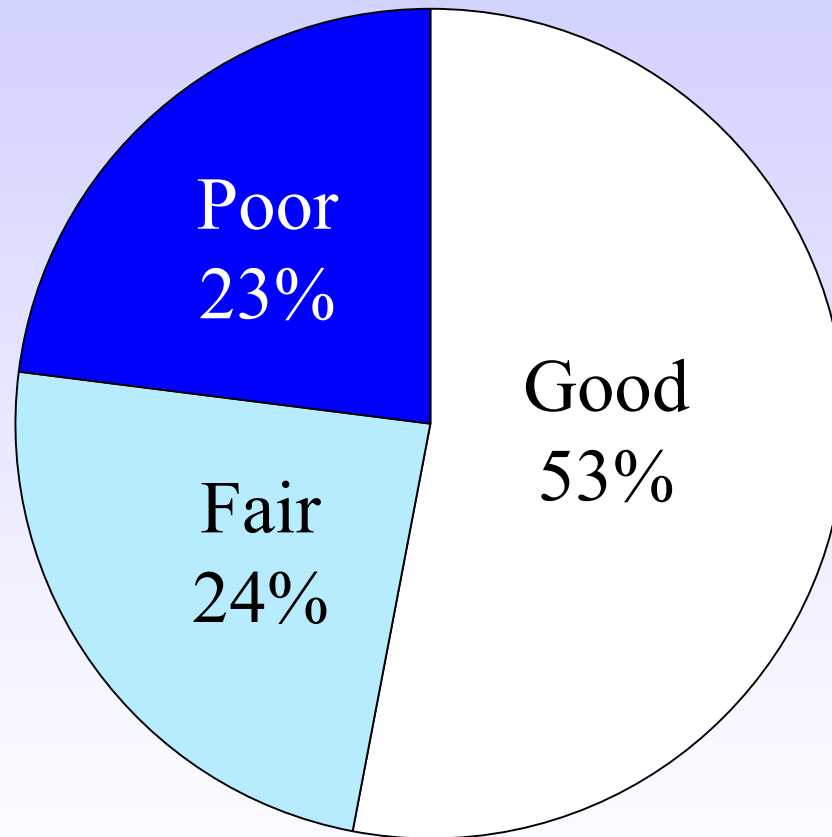
Outer ear canal type	26 ears
Attic type	54 ears
Sinus type (Pars-tensa type)	19 ears
Recurrent type	6 ears

Assessment

- Good - Condition without debris continued for at least more than a month
- Fair - Debris apparently decreased
- Poor - No change was seen

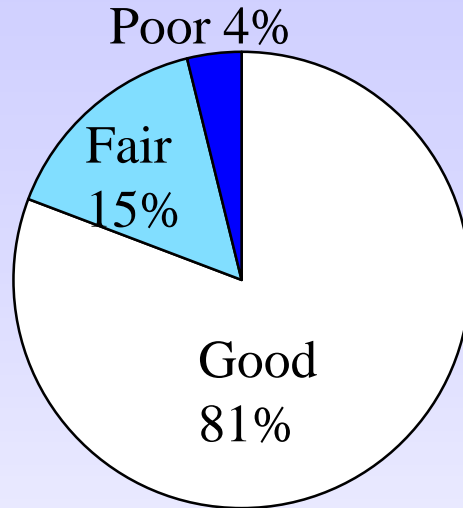


Results (105 ears)

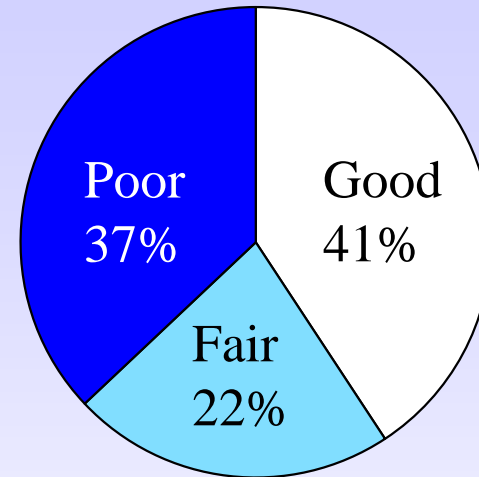


5-FU ointment was highly effective!

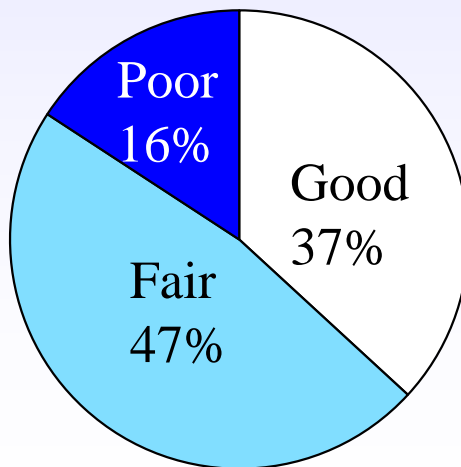
Results of 5-FU treatment in various types of cholesteatomas



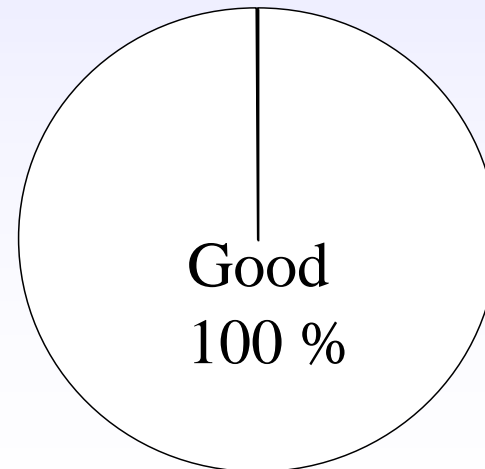
Ear canal type (26 ears)



Attic type (54 ears)



Sinus type (19 ears)

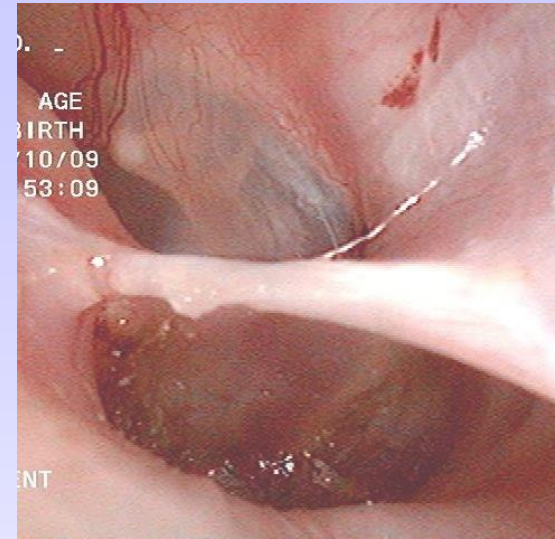


Recurrent type (6 ears)

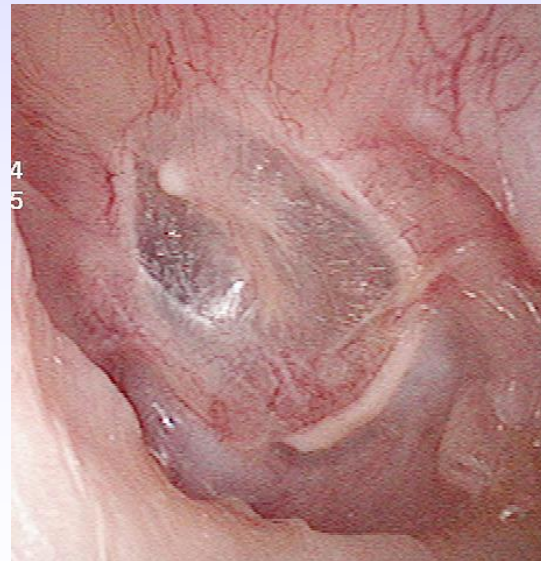
This treatment is effective
also on ear-canal
cholesteatoma!

Probably because we can see the
whole lesion and can easily clean up
before treatment.

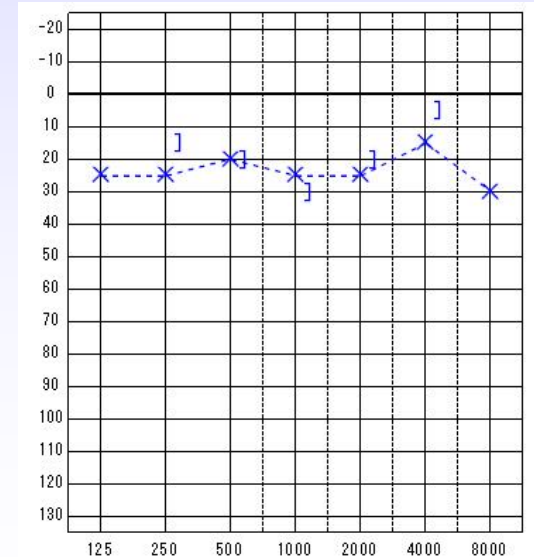
Case. EAC cholesteatoma (67 y.o., man)



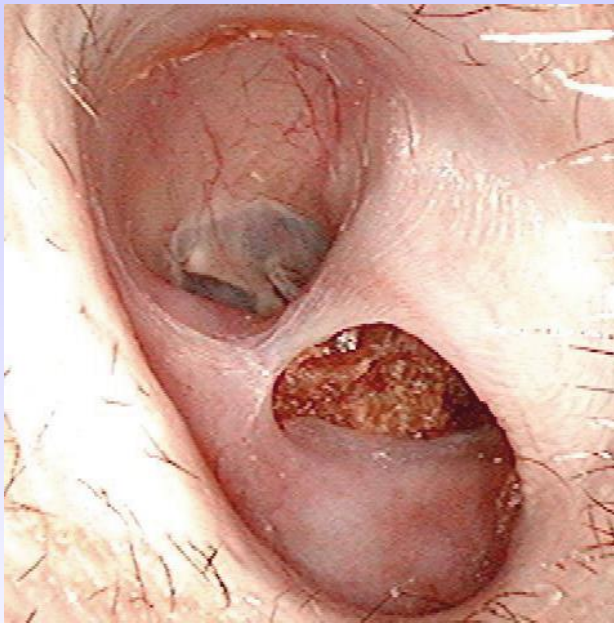
Skin bridge
was resected.



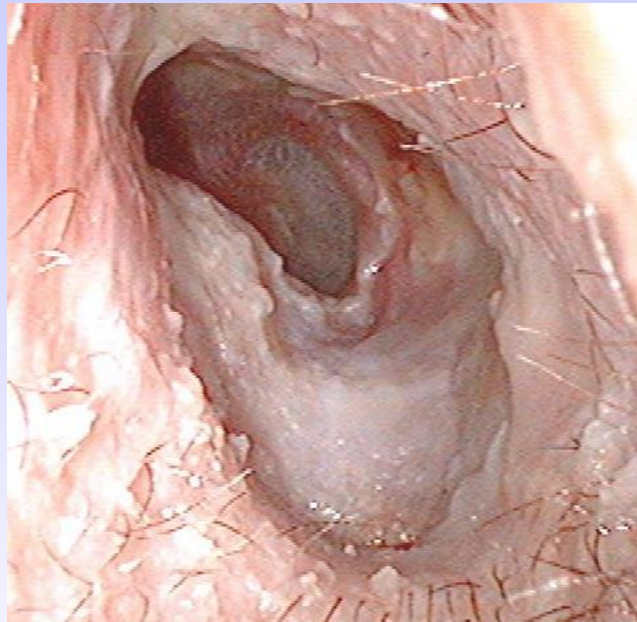
Two years later



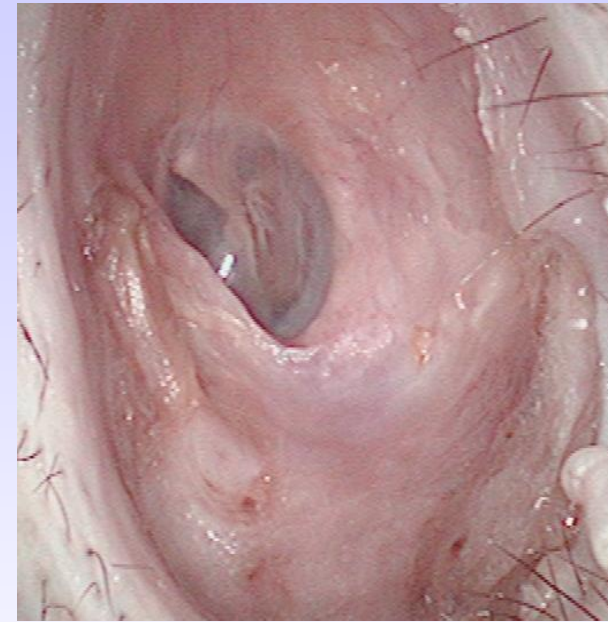
Case. EAC cholesteatoma (69 y.o., man)



First visit
After 5-FU treatment



Two months after
surgery.



One year after -
completely cured.

5-FU treatment can be used in combination with surgery,
especially for EAC cholesteatoma.

Side effects

- Hearing loss, tinnitus 0
- Erosion or ulcer formation 0

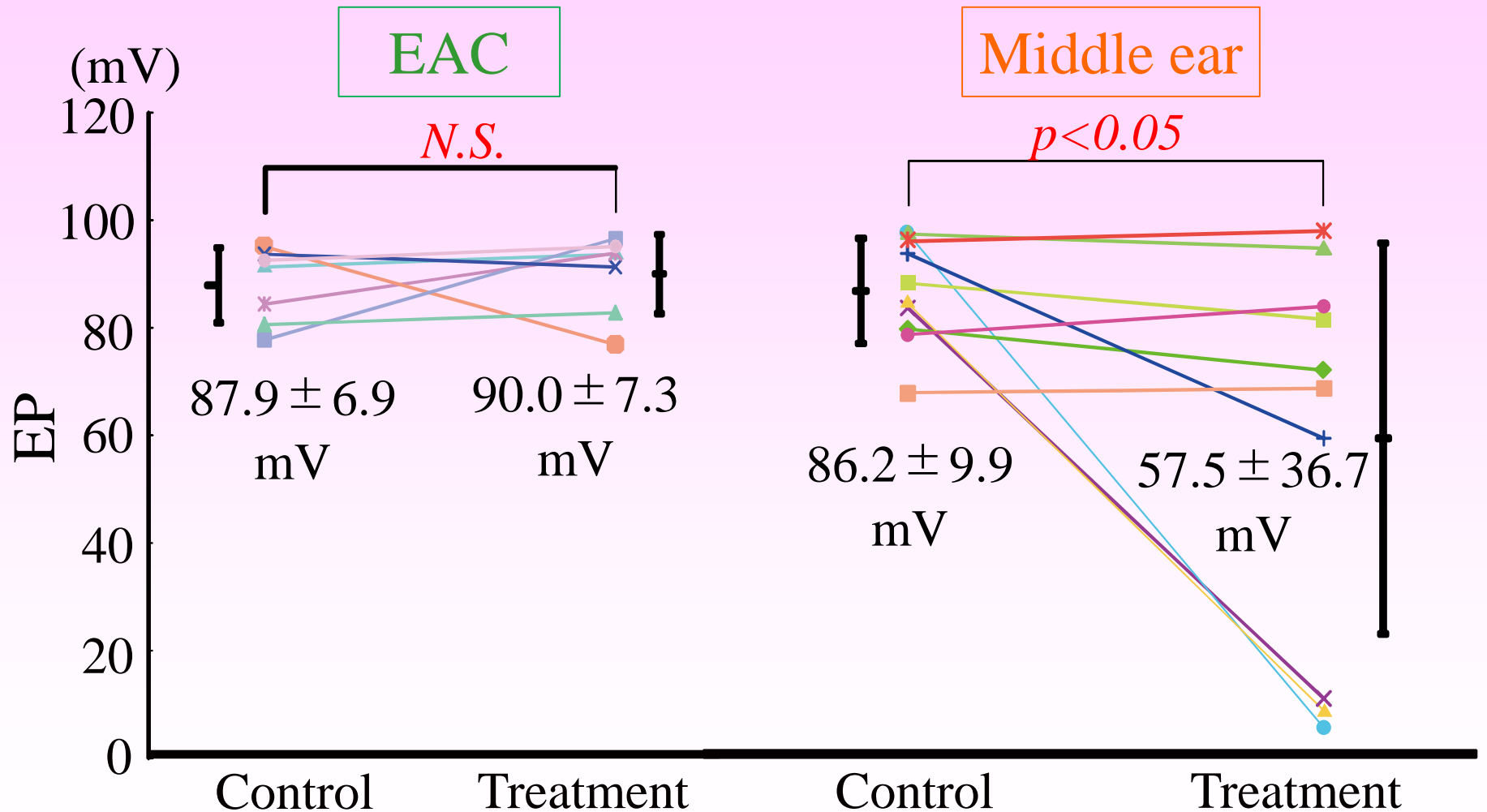


5-FU and ototoxicity?



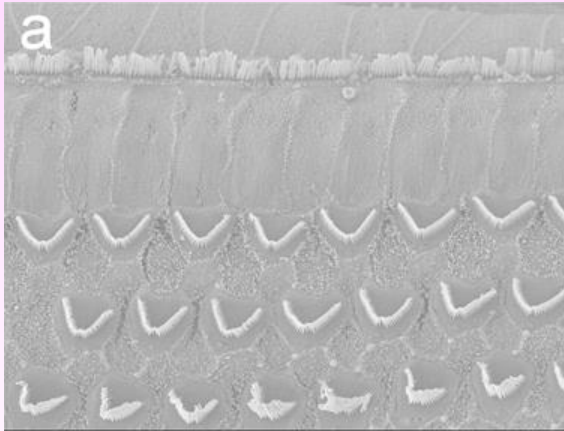
Nagasaki Lantern festival

Endocochlear potential (EP) after administration of 5-FU ointment (guinea pigs)

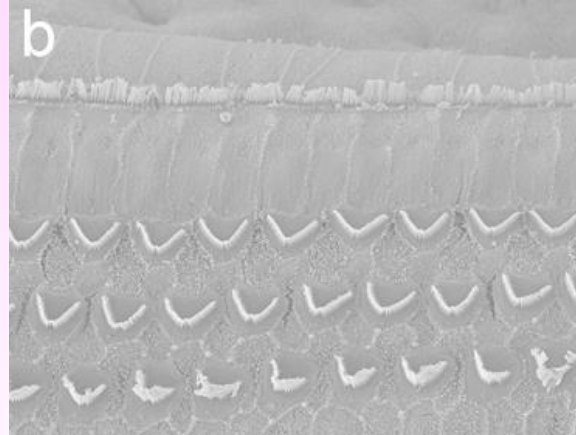


(Iwanaga, et al., Otolaryngol Head Neck Surg, 2006)

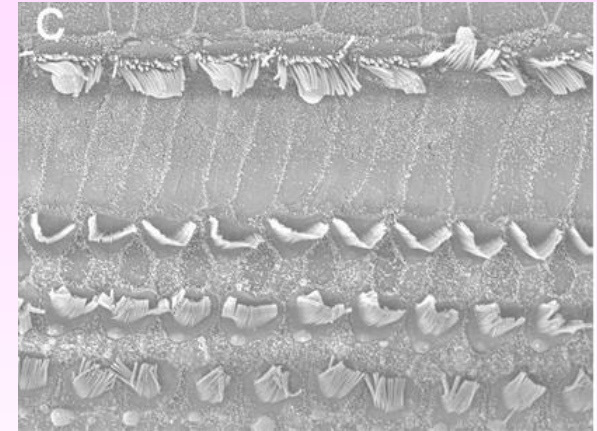
Hair cell findings one week after administration of 5-FU to middle ear



Basal turn



Middle turn



Apical turn

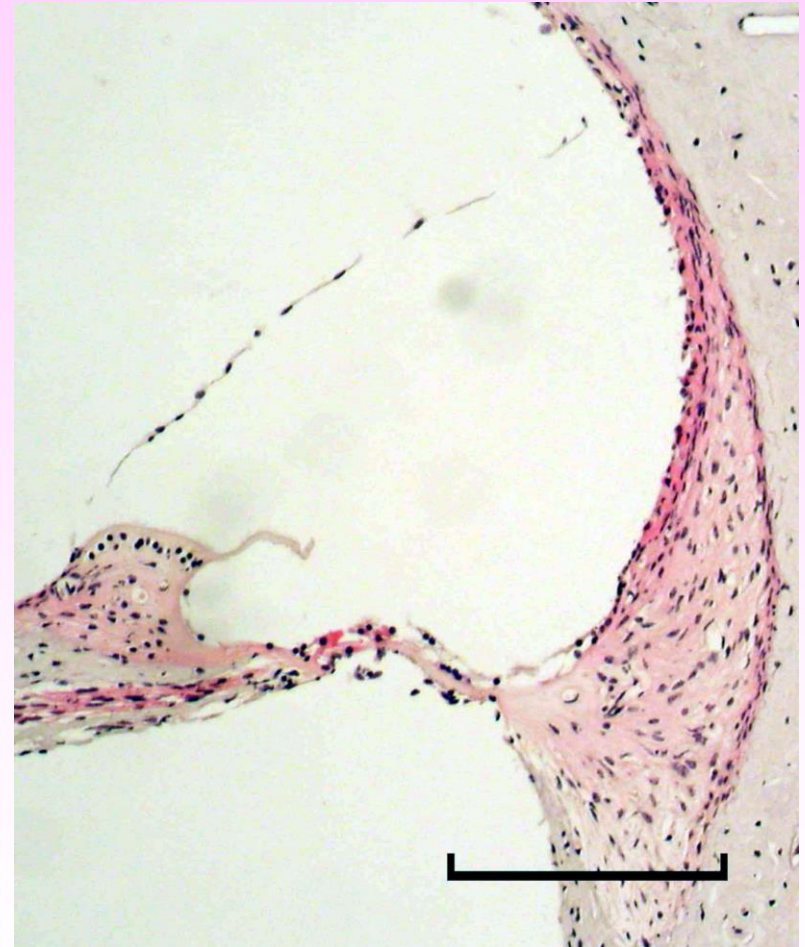
No abnormal finding on the hair cells in any turn

(Iwanaga, et al., Otolaryngol Head Neck Surg, 2006)

Light microscopic findings of the stria vascularis



Control side



Experimental side

N.S.

(Iwanaga, et al., Otolaryngol Head Neck Surg, 2006)

Mechanism of the favorable effect of 5-FU on cholesteatoma



Uncontrolled growth of cholesteatoma

Soft tissue underneath cholesteatoma
epithelium containing chronic inflammation



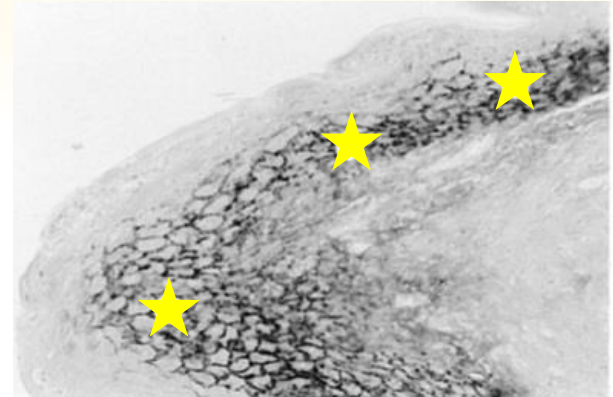
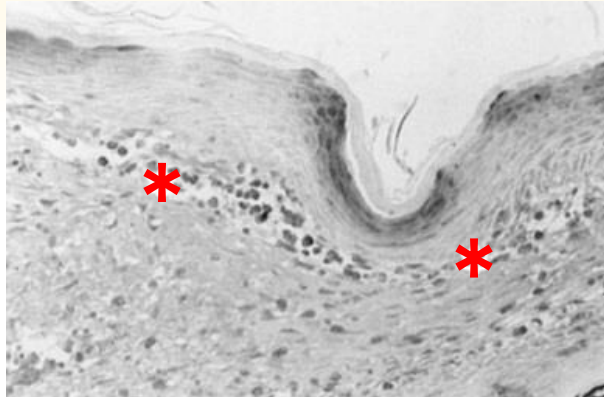
Keratinocyte growth factor (KGF)

One of the growth factors of fibroblast, and is a cytokine primarily contributing to wound healing (Finch, et al, 1989, etc.).

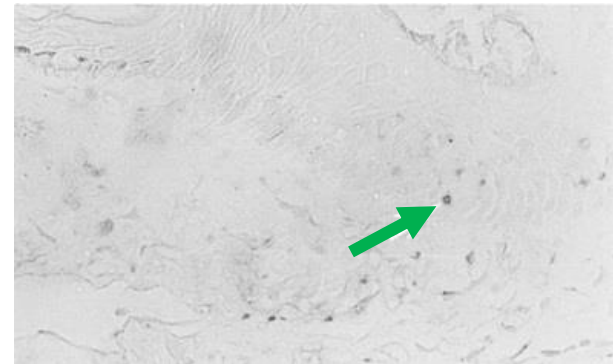
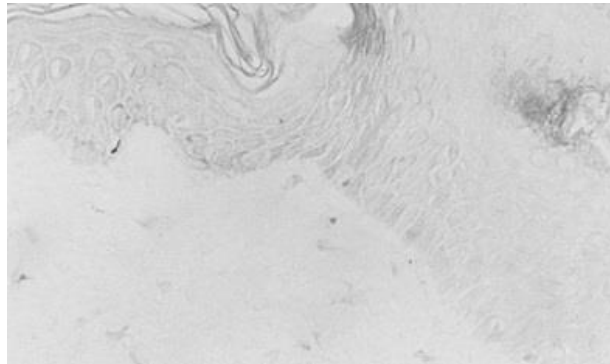
KGF and its receptor (KGFR) in cholesteatoma tissue

KGF was seen in the stroma under the epithelium, and KGFR was seen in the basal layer of the cholesteatoma epithelium.

Cholesteatoma



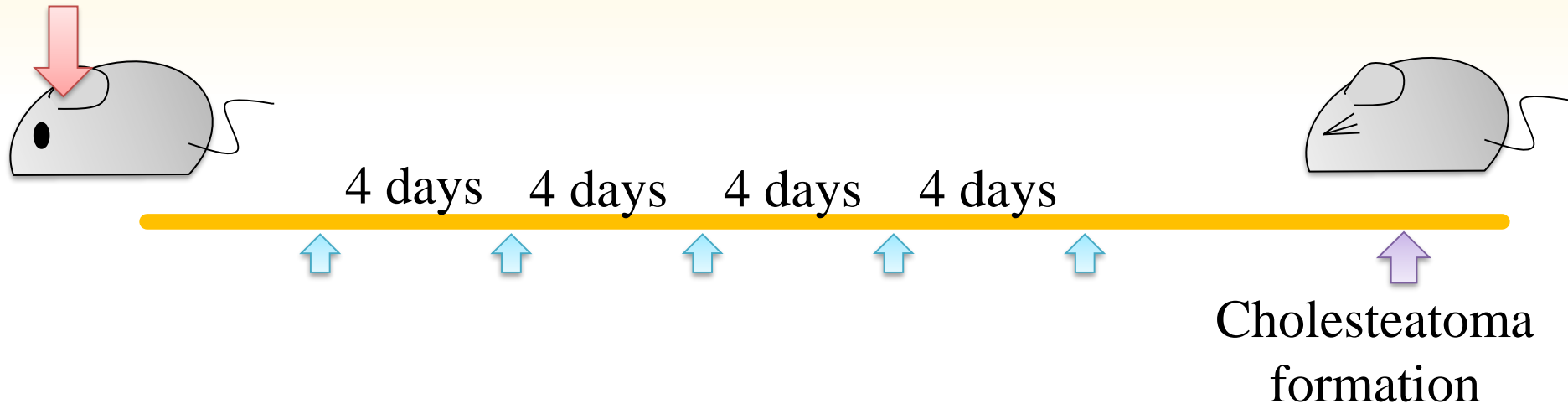
Normal ear canal skin



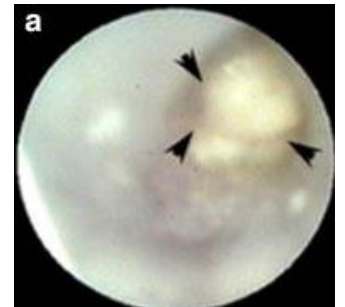
Experimental cholesteatoma with local application of KGF

Methods

Flag-hKGF vector was induced into the ear canal skin cells using electroporation in rats for 5 times.



Cholesteatoma developed in
12 out of 13 rats (92.3%)!



(Yamamoto-Fukuda T, et al., EUR Arch ORL, 2014)

Clinical study of 5-FU ointment on cholesteatoma tissue

(Yamamoto-Fukuda T, et al. Eur Arch Otorhinolaryngol 2008)

Subjects:

77 cholesteatoma patients undergoing surgery (Age 10-85)

-
1. 5-FU before surgery (12 ears)
 2. Without 5-FU treatment (65 ears)

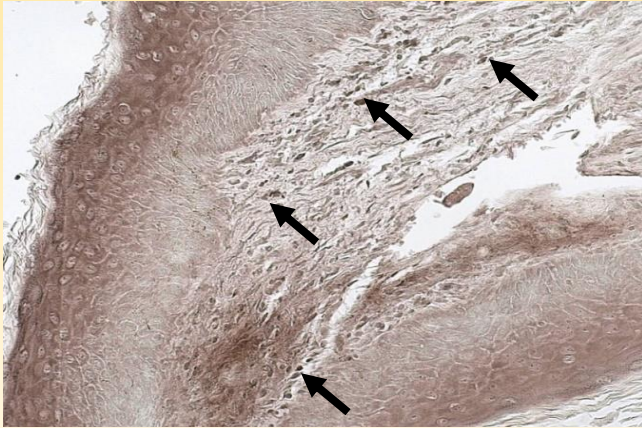
Methods:

On the resected cholesteatoma specimens, KGF and KGFR were examined by immunohistochemical method.

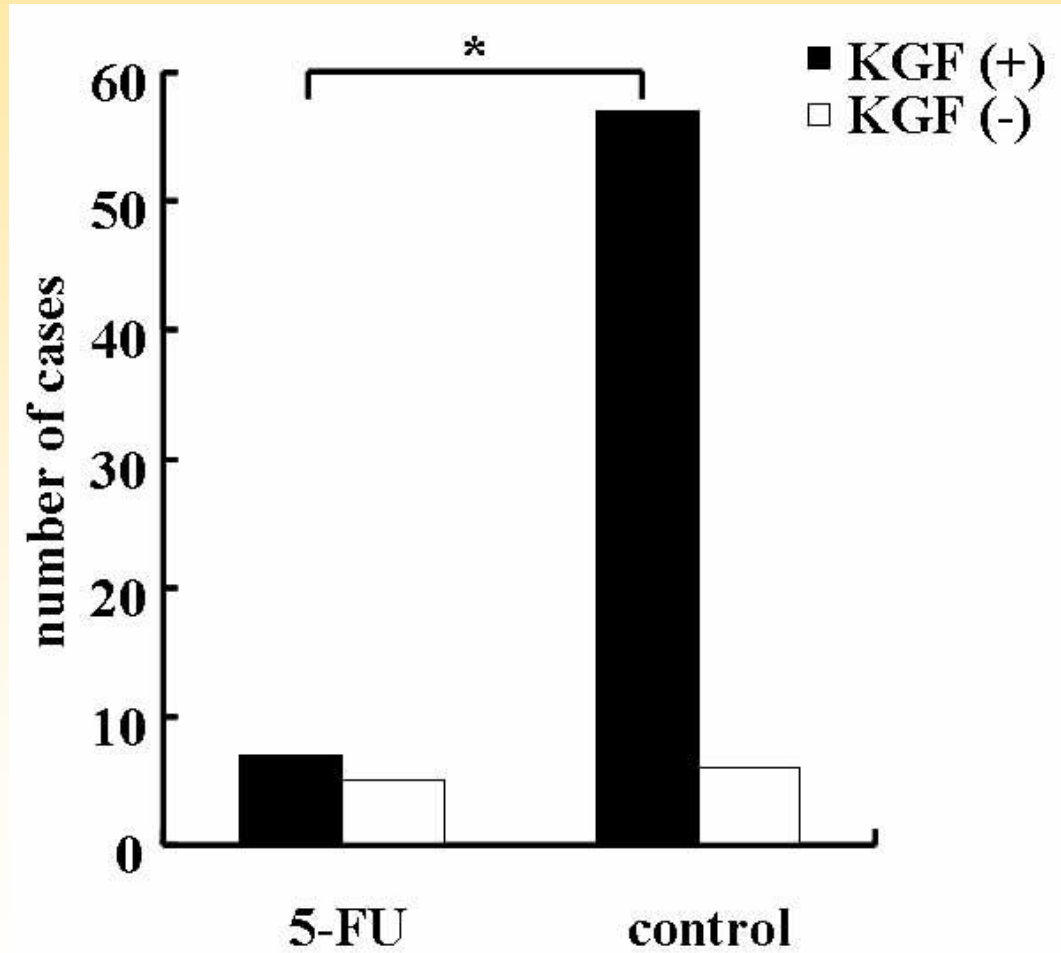
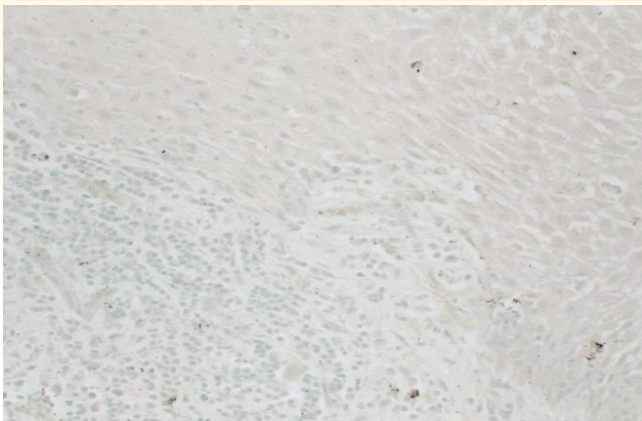
Expression of KGF in cholesteatoma tissue

5-FU treated and untreated groups

Untreated group

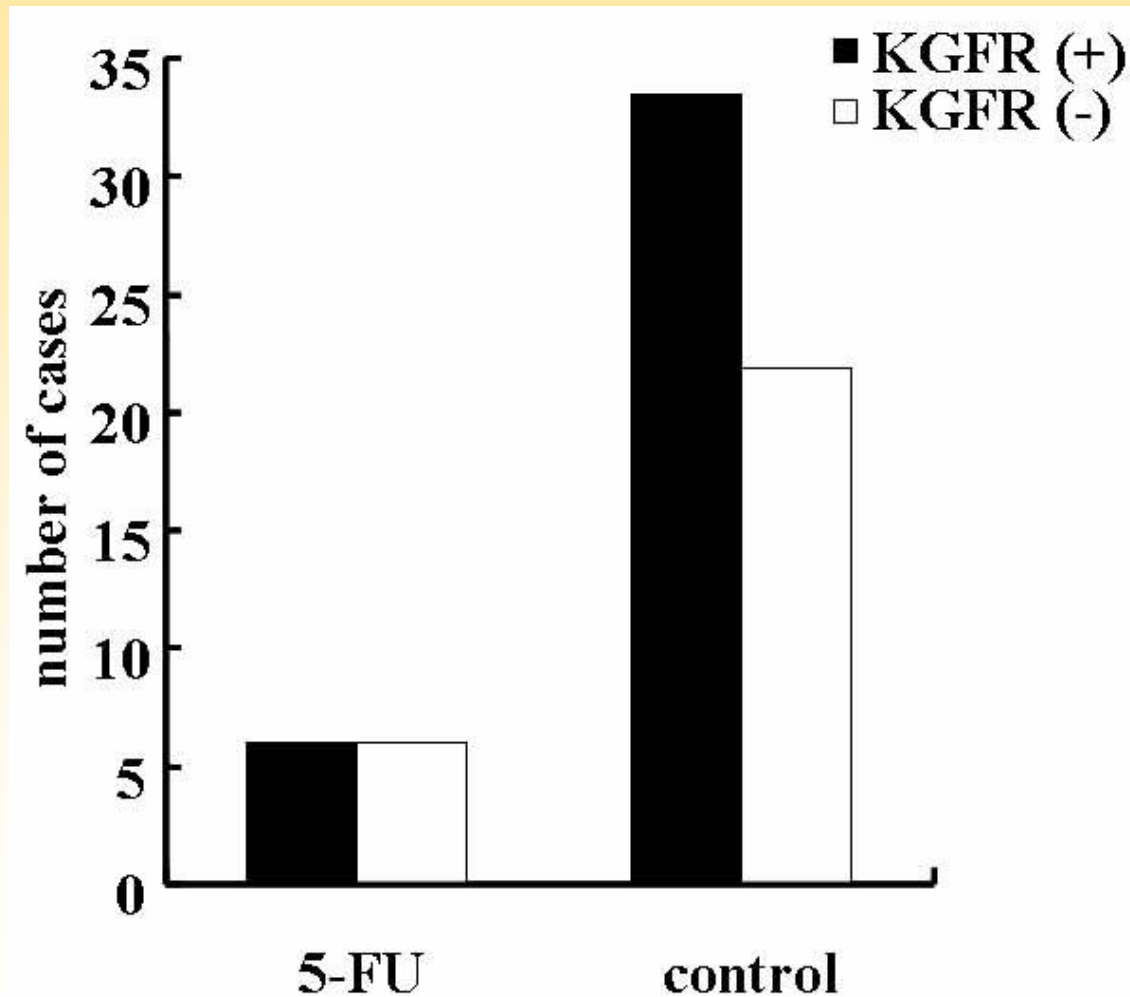


Treated group



Expression of **KGFR** in cholesteatoma tissue

5-FU treated and untreated groups



(Yamamoto-Fukuda T, et al. Eur Arch Otorhinolaryngol 2008)

Take home messages

5-FU treatment for cholesteatoma

Good for:

- Early-staged cholesteatoma
- Inoperable cases
(Underlying diseases, age, etc.)
- Those who refuse surgery

Be careful:

- Not to put it into the middle ear
- Not to apply to patients with fistula
- Periodical check by CT and audiogram

Thank you for your kind attention.



Night View
in Nagasaki