International Regulatory Forum of
Human Cell Therapy and Gene therapy Products
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Autologous hCTPs Study design

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Tokyo Women's Medical University

Today’s presentation consists of two main topics

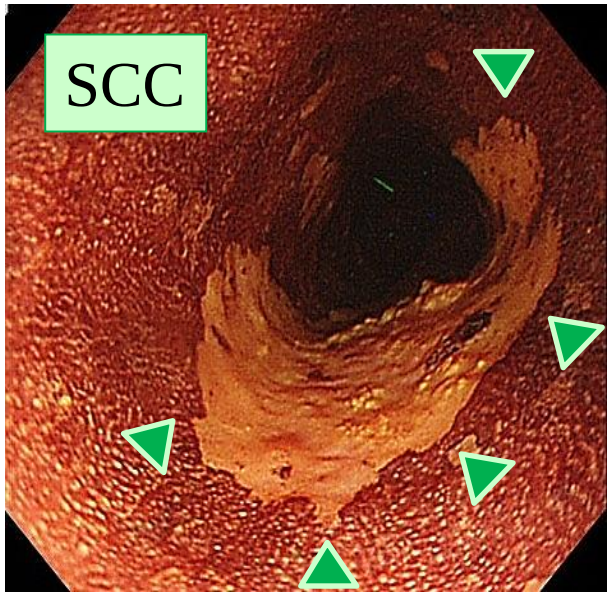
Main topics

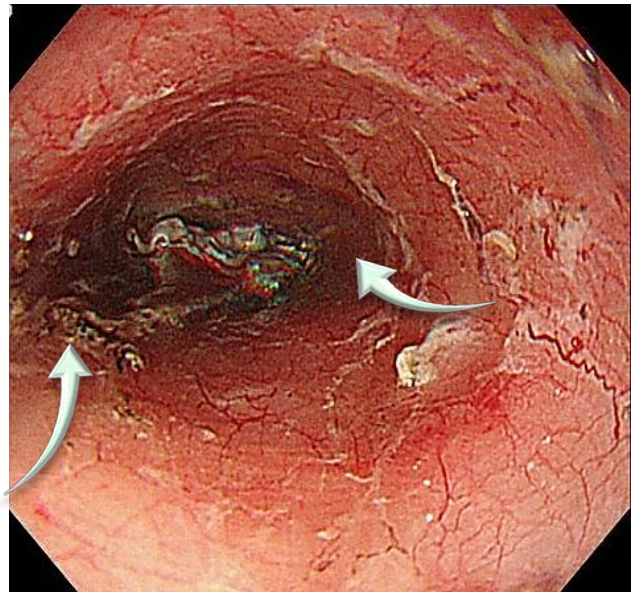
- Autologous epithelial cell sheet products
  for esophageal regeneration

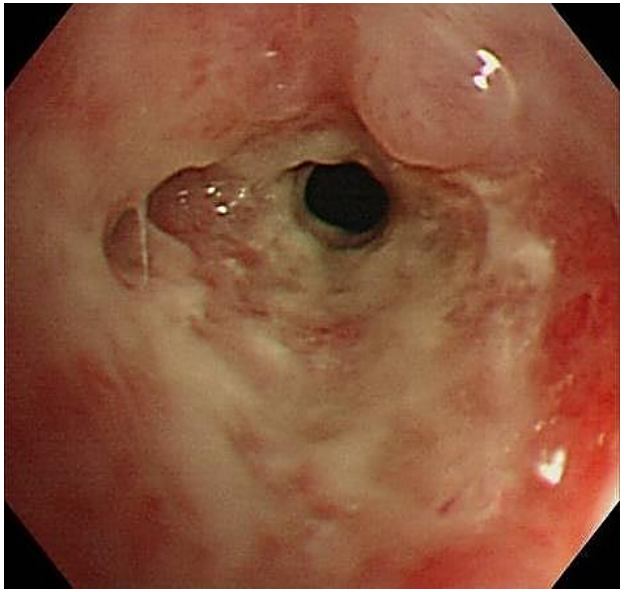
- Clinical study design
  for cell tissue products (compared with drugs)
  in Japan / Sweden

Current clinical issue

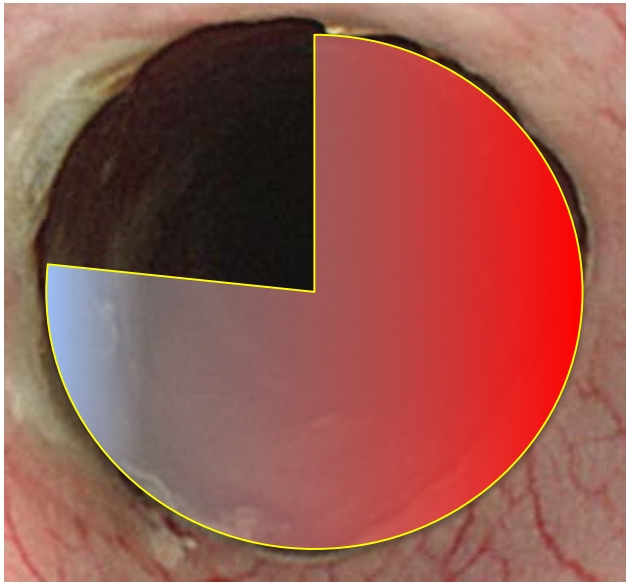
- Endoscopic submucosal dissection (ESD) involves *en bloc* removal of superficial esophageal squamous cell carcinoma (SCC).
- However, luminal stricture often occurs after ESD when the lesion involves more than three-fourth of the circumference. Frequent sessions of balloon dilatation by endoscopy is required in such situation, compromising the quality of life.







Issue 1: High frequency of complication



Resected more than 75% circumference

post-operative constriction 68-92% [1-3]

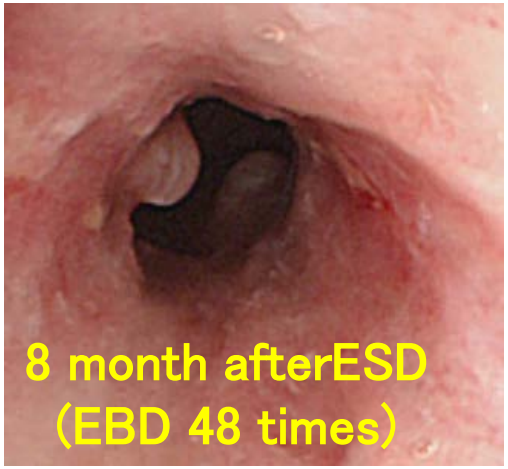
1. Ono, et al. Endoscopy 43. 661-5. 2009
2. Takahashi, et al. Endoscopy 43. 184-9. 2011
3. Ezoe, et al. J Clin Gastroenterology. 45. 222-7. 2011

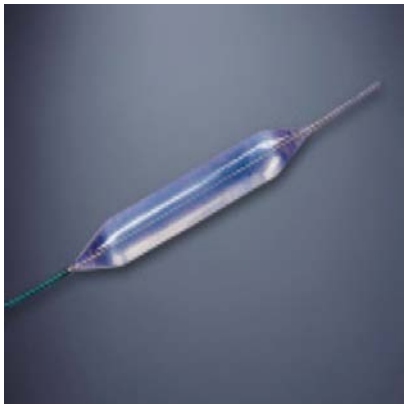
Issue 2: Refractory complication

Standard treatment for constriction

Endoscopic balloon Dilatation (EBD)

Expensive medical treatment fee
K522-3　12480 (￥124,800)





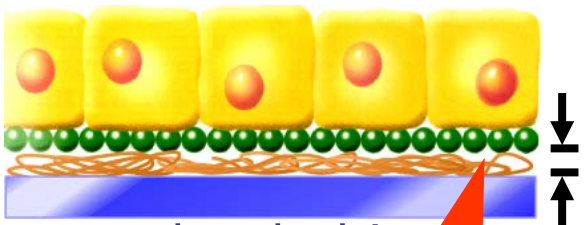
Quantum TTC®
Esophageal Balloon Dilator

Refractory esophageal constricture

Full-Circumferential ESD (100%)
32.7 times EBD
Semi-circumferential ESD (>75%)
11.0 times EBD

Cell Sheet Engineering

Cell Sheet formation
On Culture Dishes

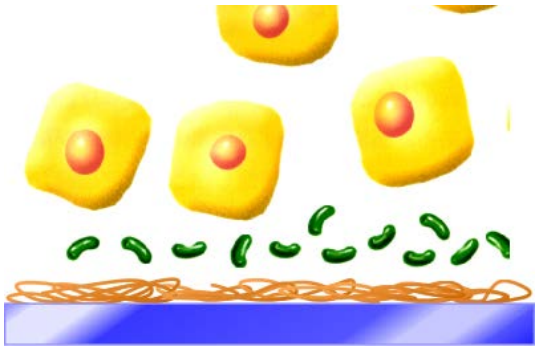


Hydrophobic
Surfaces

Temp. Responsive Polmer
Poly(*N*-isopropylacrylamide)
(PIPAAm)

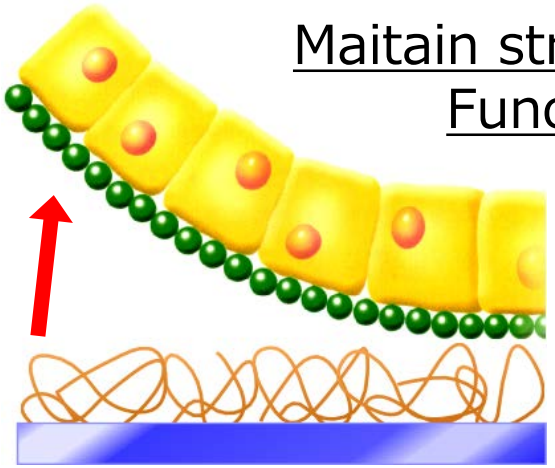
Enzyme
Treatment

Desruption of structure
and Functions



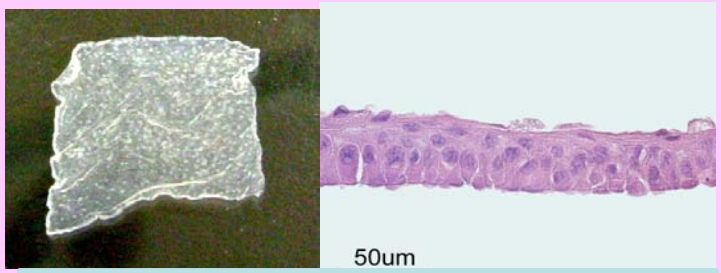
T Changes
(37→20℃)

Maitain structure and
Functions



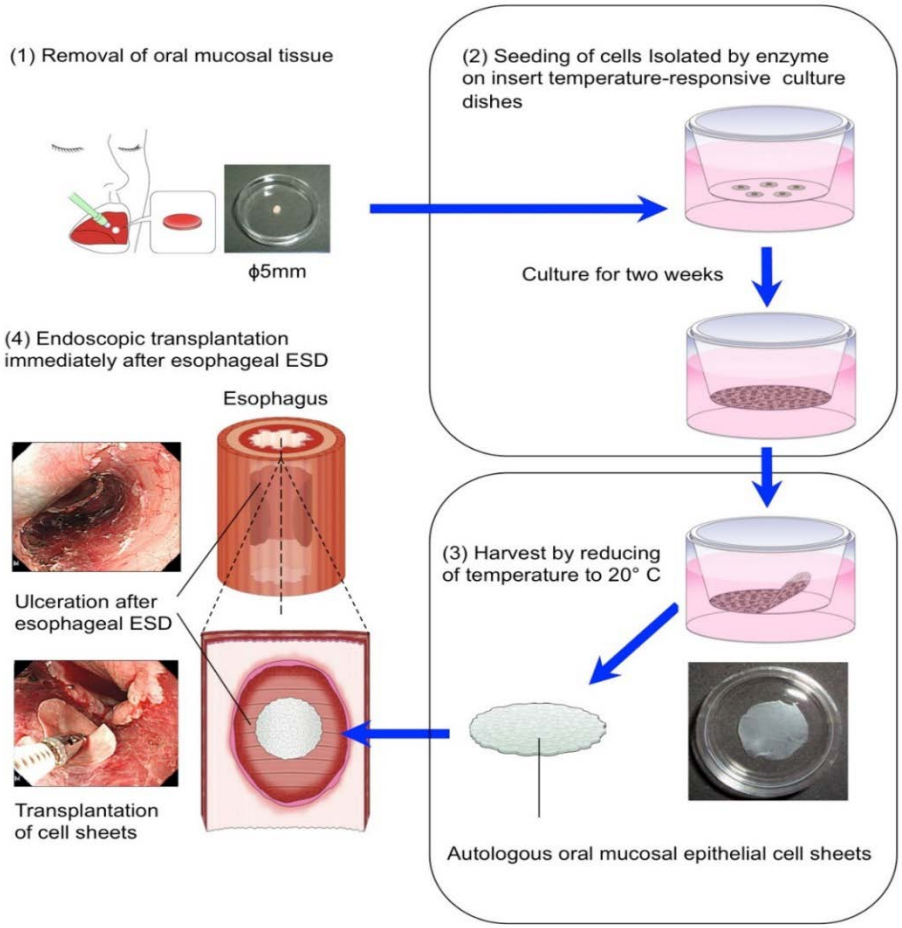
Our
Invention

Hydrophphilic
Surfaces



Oral epithelial cell sheet

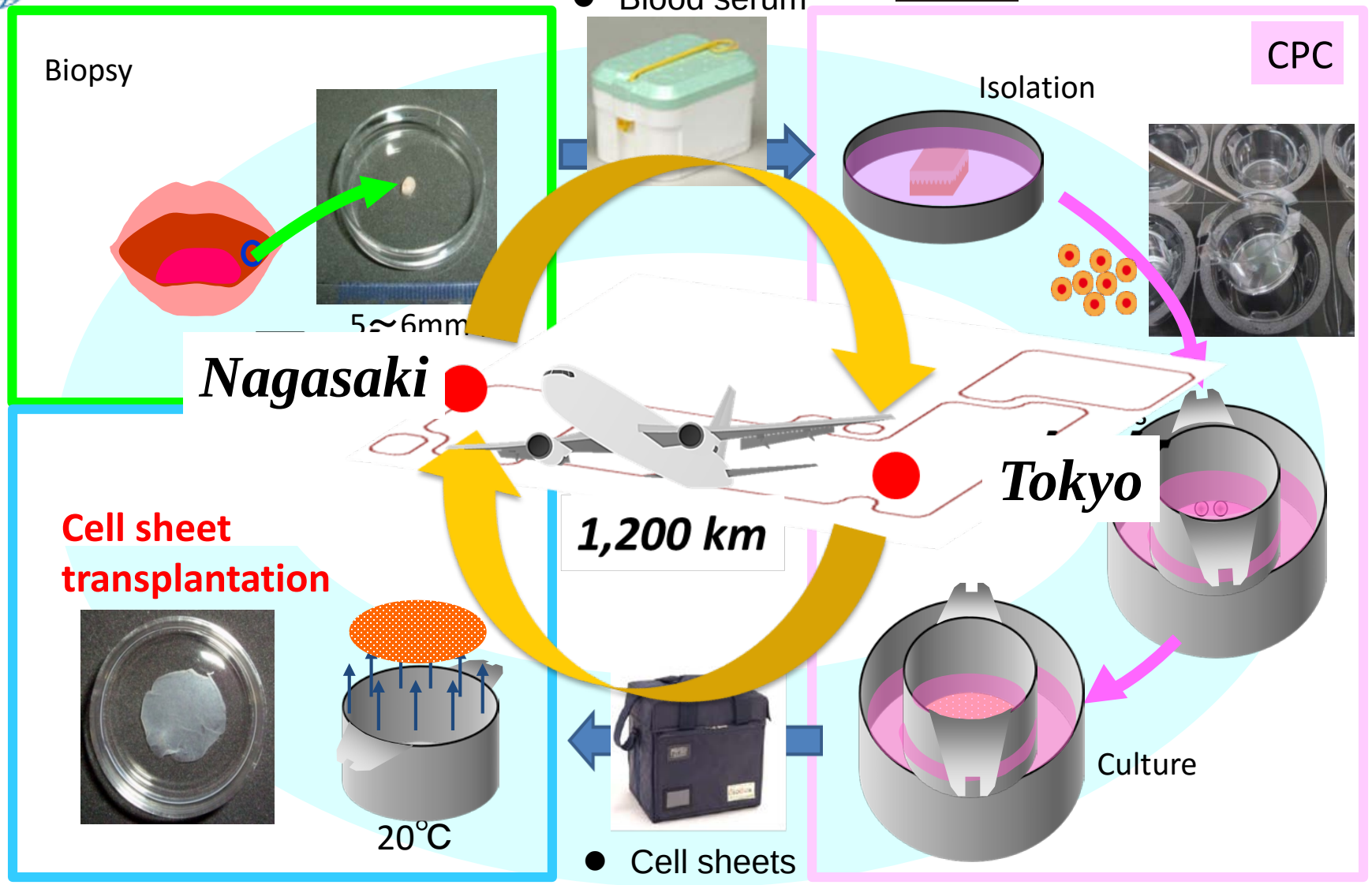
First in Human study (2008~2010)



Ohki, Yamato, et al. Gastroenterology. 2012

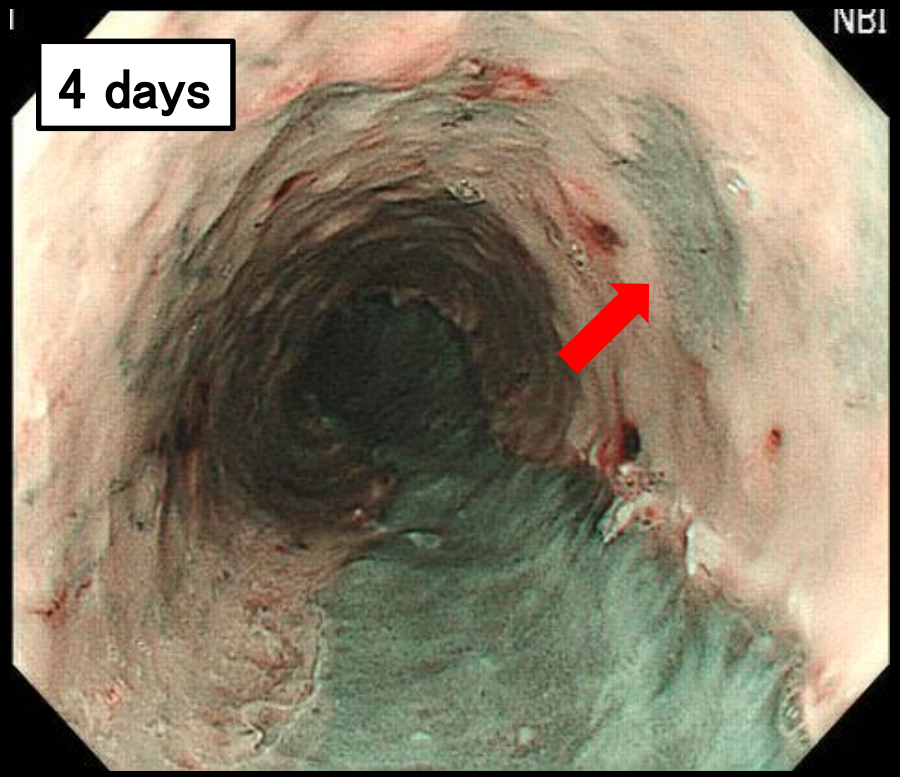
UMIN ID	UMIN000000473
Title of the study	Treatment of artificial esophageal ulcerations after EMR by endoscopic transplantation of autologous oral mucosal epithelial cell sheets
condition	Artificial esophageal ulceration after EMR
objectives	To establish the procedure Safety, Efficacy exploratory
Primary outcome	The size of ulceration
Secondary outcome	Adverse event
Study design	Single arm Not randomized
Target sample size	10

Clinical study : 10 cases (2013~2014)

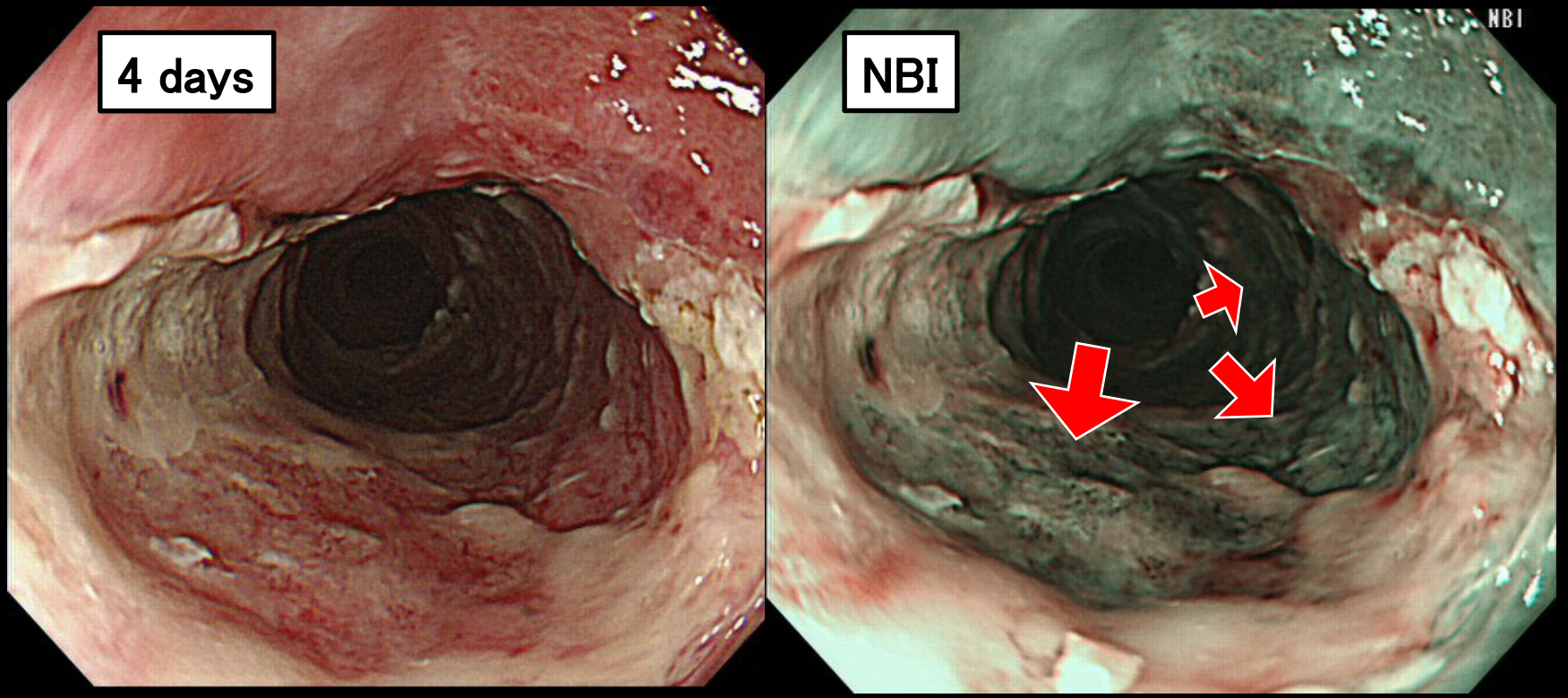


UMIN ID	UMIN000002846
Title of the study	Safety and efficacy of transplantation of oral mucosal epithelial cell sheets in preventing formation of stricture after ESD
condition	Superficial esophageal cancer
objectives	Safety, Efficacy
Primary outcome	Morbidity Stricture
Secondary outcome	Adverse event
Study design	Single arm Histrical control
Target sample size	10
Progress	Completed 2013-2014

Conventional transplantation (with support membrane)



Cell sheets transplantation with dedicated device



6 cell sheets transplanted using a new dedicated device

Dedicated delivery device

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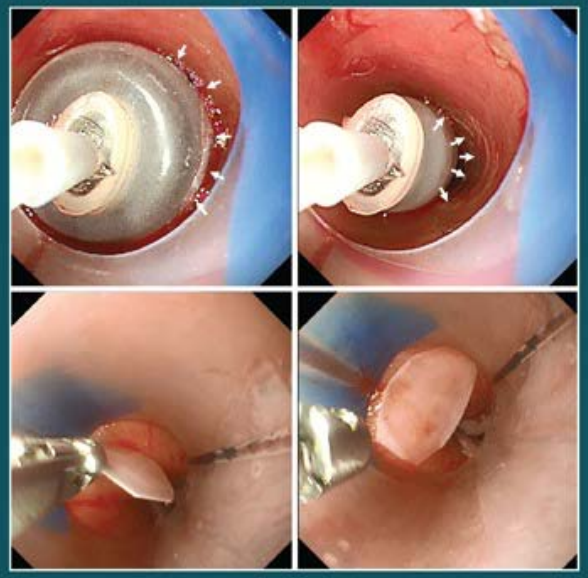
GIE

Gastrointestinal Endoscopy



Single-balloon enteroscopy-assisted ERCP in patients with surgically altered GI anatomy

Value of EGD in patients referred for cholecystectomy

Features of sessile serrated adenomas by using narrow-band imaging with optical magnification

Survival in colorectal cancer patients diagnosed by screening colonoscopy

ELSEVIER
www.giejournal.org
ASGE members: www.asge.org

NEW METHODS

Endoscopic cell sheet transplantation device developed by using a 3-dimensional printer and its feasibility evaluation in a porcine model

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Nagasaki, Tokyo, Japan

Background: To prevent severe esophageal stenosis after aggressive endoscopic submucosal dissection (ESD), our group previously reported an efficient treatment using cell sheets that had been fabricated from patient cells. However, this transplantation procedure had not been easy for every endoscopist and needed to be improved to derive the full effect of epithelial cell sheets.

Objective: To develop an endoscopic device that enables easy and effective cell sheet transplantation and to evaluate its performance and clinical feasibility.

Design: Animal study.

Setting: Animal experimentation laboratory.

Intervention: Three pigs underwent circumferential esophageal ESD while under general anesthesia. A total of 12 cell sheets were endoscopically transplanted to the ESD site; 6 cell sheets were transplanted by using an endoscopic device that we developed, and 6 cell sheets were transplanted by using the conventional method.

Main Outcome Measurements: Procedure time, transplanted area on the ESD site, transplantation success rate, and monitoring of adverse events or incidents.

Results: The device allowed successful transplantation of all cell sheets with a shorter procedure time than with the conventional method (4.8 ± 0.8 minutes vs 13.3 ± 5.7 minutes, respectively) ($P = .005$) and onto a larger area (111.3 ± 56.3 mm^2 vs 41.8 ± 4.2 mm^2, respectively) ($P = .023$) with a higher success rate (100% vs 83%, respectively). No adverse incidents were monitored in each method.

Limitations: Animal study, small sample.

Conclusion: A newly designed endoscopic cell sheet transplantation device would be useful.

BACKGROUND

Esophageal stenosis is one of the major adverse events after aggressive endoscopic submucosal dissection (ESD) for early-stage esophageal cancer.[1-4] For treating stenosis, endoscopic balloon dilation has been widely used, although repeated stenosis is still an issue.[5] Clinical research involving steroid therapies[6,7] and stent treatments[2,8,9] have been studied to overcome esophageal stenosis after aggressive ESD.

Abbreviation: ESD, endoscopic submucosal dissection.

DISCLOSURE: *Dr Okano is a founder of CellSeed Inc, is a member of the Board of Directors of CellSeed Inc and has licensed technologies and patents from Tokyo Women's Medical University related to this study and is a shareholder in CellSeed Inc. Dr Yamato is a consultant and shareholder in CellSeed Inc. All other authors disclosed no financial relationships relevant to this article. This study was supported by Grant-in-Aid for Scientific Research B (14483609 to Dr Kanai), Cell Sheet Tissue Engineering Center (CSTEC), The Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Program" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and a Health Labor Scientific Research Grants (26220103 to Dr Okano and 26270803 to Dr Yamato).*

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http://dx.doi.org/10.1016/j.gie.2015.01.062

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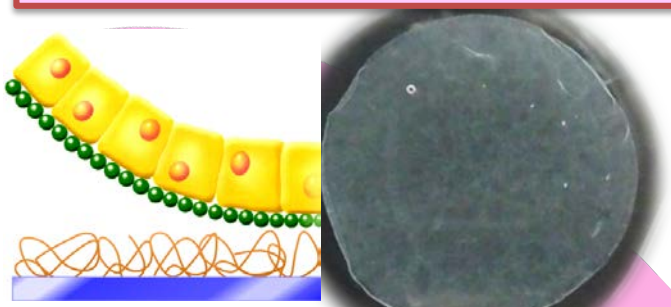
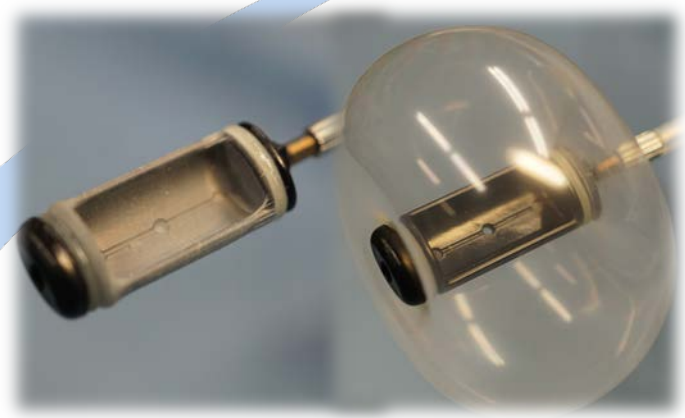
(footnotes continued on last page of article)

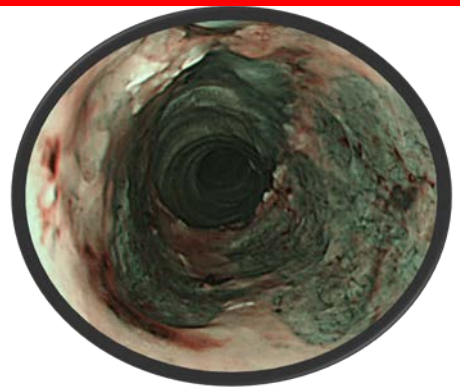
Tissue-engineered
Epithelial cell sheet

Dedicated
delivery device





Specialized Cell Sheet Delivery Technique



1:TWMU (2008~2010)

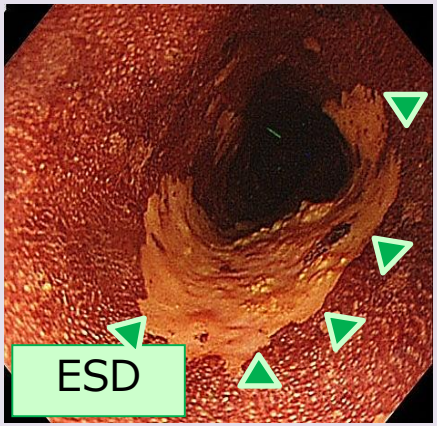
No	Age Gender	Circum. (%)	Resected Size	Resected Area	Cell Sheets	Stenosis	Balloon (times)
1	70 M	67	43㎜	1548㎜^{2}	2	—	0
2	73 M	67	21㎜	231㎜^{2}	2	—	0
3	73 M	67	43㎜	645㎜^{2}	3	—	0
4	65 M	100	55㎜	3850㎜^{2}	7	+	21
5	64 M	50	24㎜	552㎜^{2}	2	—	0
6	55 M	75	45㎜	1800㎜^{2}	7	—	0
7	80 M	67	43㎜	1204㎜^{2}	8	—	0
8	70 M	75	45㎜	1350㎜^{2}	4	—	0
9	68 M	75	42㎜	1260㎜^{2}	6	—	0

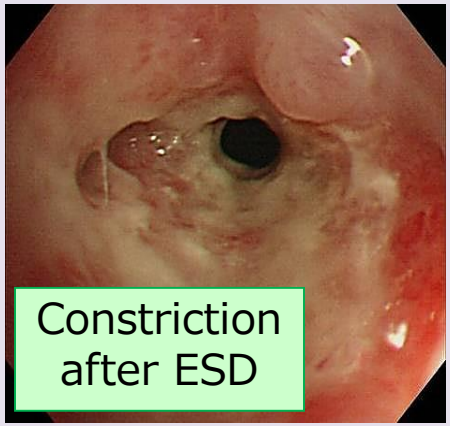
2:NAGASAKI＆TWMU (2013~2014)

No	Age Gender	Circum. (%)	Resected Size	Resected Area	Cell Sheets	Stenosis	Balloon (times)
1	55 M	88	80㎜	4400㎜^{2}	6	－	0
2	68 M	90	75㎜	5200㎜^{2}	7	＋	1
3	73 M	83	45㎜	1350㎜^{2}	5	－	0
4	58 M	88	55㎜	2530㎜^{2}	8	＋	2
5	67 M	83	50㎜	1650㎜^{2}	8	－	0
6	56 M	83	55㎜	2200㎜^{2}	6	－	0
7	63 M	90	103㎜	4015㎜^{2}	8	－	0
8	72 M	100	95㎜	5985㎜^{2}	13	＋	7
9	62 M	100	50㎜	2650㎜^{2}	5	＋	1
10	74 M	88	46mm	2070㎜^{2}	6	－	0

Results(1+2)

No	Age Gender	Circum. (%)	Resected Size	Resected Area	Cell Sheets	Stenosis	Balloon (times)
1	70 M	67	43㎜	1548㎜^{2}	2	−	0
2	73 M	67	21㎜	231㎜^{2}	2	−	0
3	73 M	67	43㎜	645㎜^{2}	3	−	0
4	65 M	100	55㎜	3850㎜^{2}	7	+	21
5	64 M	50	24㎜	552㎜^{2}	2	−	0
6	55 M	75	45㎜	1800㎜^{2}	7	−	0
7	80 M	67	43㎜	1204㎜^{2}	8	−	0
8	70 M	75	45㎜	1350㎜^{2}	4	−	0
9	68 M	75	42㎜	1260㎜^{2}	6	−	0
1	55 M	88	80㎜	4400㎜^{2}	6	−	0
2	68 M	90	75㎜	5200㎜^{2}	7	+	1
3	73 M	83	45㎜	1350㎜^{2}	5	−	0
4	58 M	88	55㎜	2530㎜^{2}	8	+	2
5	67 M	83	50㎜	1650㎜^{2}	8	−	0
6	56 M	83	55㎜	2200㎜^{2}	6	−	0
7	63 M	90	103㎜	4015㎜^{2}	8	−	0
8	72 M	100	95㎜	5985㎜^{2}	13	+	7
9	62 M	100	50㎜	2650㎜^{2}	5	+	1
10	74 M	88	46mm	2070㎜^{2}	6	−	0





No treatment

More than 75% cir. ESD

→Constriction rate 68～92%

→Refrectory stenosis

Cell sheets transplantation

More than 75% cir. ESD

→Constriction rate 34%

→Refrectory stenosis ↓

Clinical trial

Clinical development of epithelial cell sheet for esophageal regeneration

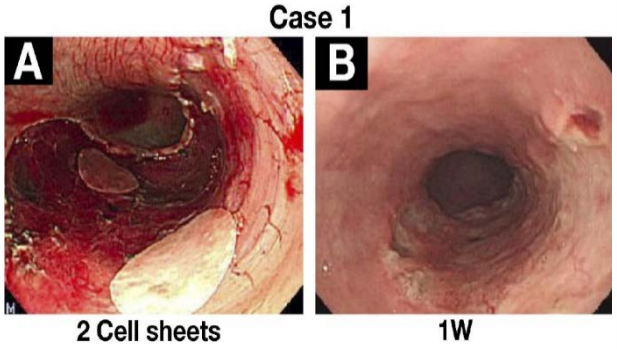
Clinical research in academia

Tokyo Women's Medical University

Japan : Tokyo Women's Medical University 20 patients
Sweden : Karolinska University Hospital 10 patients

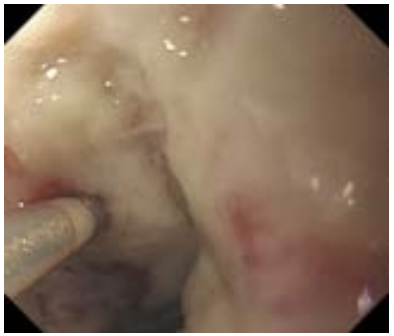
Company sponsored clinical trial

Japan ⟷ CellSeed ⟷ Europe



Treatments for avoiding constriction

- **Triamsinolone injection**



Hashimoto, et al.GIE 2011

- **Oral prednisolone administraion**

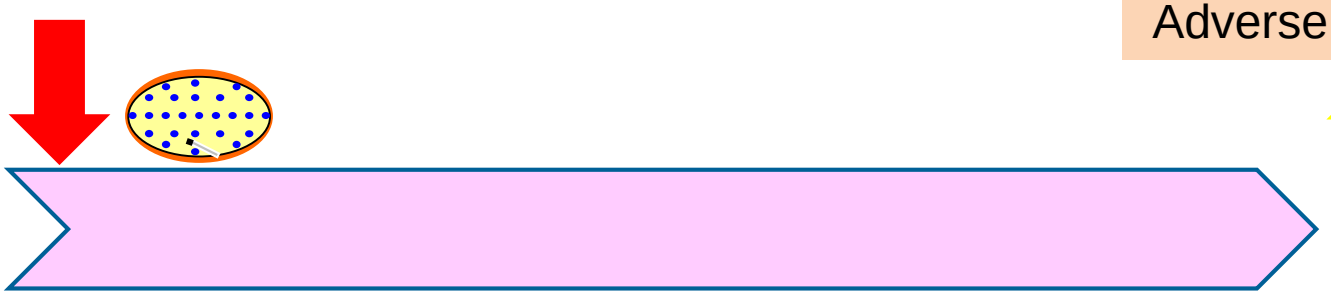
Yamaguchi. Isomoto, et al.GIE 2011

JCOG 1217

UMIN ID	UMIN000015064
Title of the study	A phase III study of oral steroid administration versus local steroid injection therapy for the prevention of esophageal stricture after ESD (JCOG1217, Steroid EESD P3)
condition	Early stage esophageal cancer after ESD
objectives	To confirm the superiority Safety, Efficacy Phase III
Primary outcome	Stricture-free survival
Secondary outcome	The number of EBD for 12 weeks
Study design	Parallel, Randomized
Target sample size	**360**
Progress	Open public recruiting 2014.9-2018.3

Triamsinolone injection group

Day 0: treatment

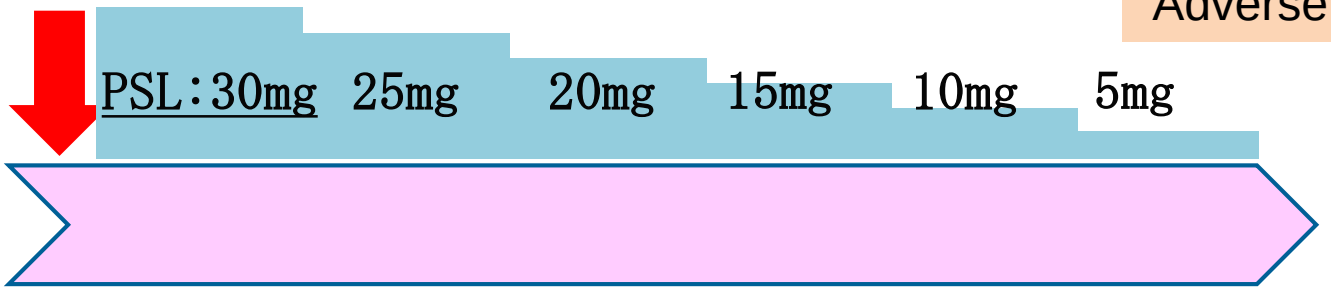


12 weeks:
Adverse event

Less than 5cm ESD

Oral prednisolone administration group

Day 0: treatment

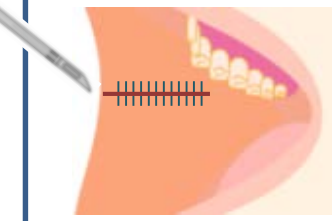


12 weeks:
Adverse event

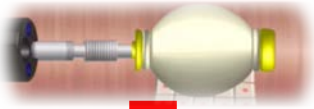
Less than 5cm ESD

Autologous epithelial cell sheet (in Japan)

Biopsy



Day 0: treatment



12 weeks: Esophageal stenosis rate

Cell culture for 14 days

CPF

More than 75% circumference ESD

Single arm study design

No treatment

- Biopsy…
- Hard end point…

No treatment → High frequency of stenosis

More than 75% circumference ESD

In conclusion

- Cell sheet product has an uniquely potential.

- Clinical study of hCTPs should be designed to compare the status of each disease case-by-case.