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Clinical Trial Results

Phase II Trial of 5-Fluorouracil, Docetaxel, and Nedaplatin (UDON) Combination Therapy for Recurrent or Metastatic Esophageal Cancer

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Trial Information

- **Trial Identifier**: UMIN000017685
- **Sponsor(s)**: None
- **Principal Investigator**: Kazuhiko Nakagawa
- **IRB Approved**: Yes

Lessons Learned

- The 5-fluorouracil, docetaxel, and nedaplatin (UDON) regimen was well tolerated and showed promising antitumor activity in terms of both objective response rate and survival for patients with advanced or recurrent esophageal squamous cell carcinoma in the first-line setting.
- UDON may be an optimal treatment option for patients with advanced esophageal cancer who are unfit for docetaxel, cisplatin, and 5-fluorouracil regimens.
- The high response rate as well as the rapid and marked tumor shrinkage associated with UDON suggest that further evaluation of this regimen in the neoadjuvant setting is warranted.

Abstract

Background. A phase II study was performed to evaluate the efficacy and safety of 5-fluorouracil (5-FU), docetaxel, and nedaplatin (UDON) combination therapy for untreated recurrent or metastatic esophageal cancer.

Methods. Patients received intravenous nedaplatin (90 mg/m^2) on day 1, docetaxel (35 mg/m^2) on days 1 and 15, and 5-fluorouracil (800 mg/m^2) on days 1–5 of a 4-week cycle. The primary endpoint was response rate, with secondary endpoints including overall survival (OS), progression-free survival (PFS), dysphagia score, and adverse events.

Results. Between March 2015 and July 2017, 23 patients were enrolled. Of 22 evaluable patients, 16 and 4 individuals experienced a partial response and stable disease, respectively, yielding a response rate of 72.7% (95% confidence interval [CI], 49.8%–89.3%) and disease control rate of 90.9% (95% CI, 70.8%–98.9%). Median OS and PFS were 11.2 months (95% CI, 9.1 months to not reached) and 6.0 months (95% CI, 2.5–10.6 months), respectively. Eleven (64.7%) of the 17 patients with a primary lesion showed amelioration of dysphagia after treatment. Frequent adverse events of grade 3 or 4 included neutropenia (87.0%) and leukopenia (39.1%). Febrile neutropenia was observed in two patients (8.7%).

Conclusion. This phase II study demonstrated promising antitumor activity and good tolerability of UDON. ***The Oncologist*** 2019;24:163–e76

Discussion

In the present study, the efficacy and safety of the UDON regimen was evaluated as first-line treatment for Japanese patients with advanced or recurrent esophageal cancer (all of whom had squamous cell carcinoma). Consistent with the results of a previous phase I study [1], a high antitumor activity of UDON was found, with an overall response rate (RR) of 72.7%, which is likely equivalent to that for 3- or 4-weekly DCF (docetaxel, cisplatin, and 5-FU) [2] and possibly higher than that for weekly [3] or

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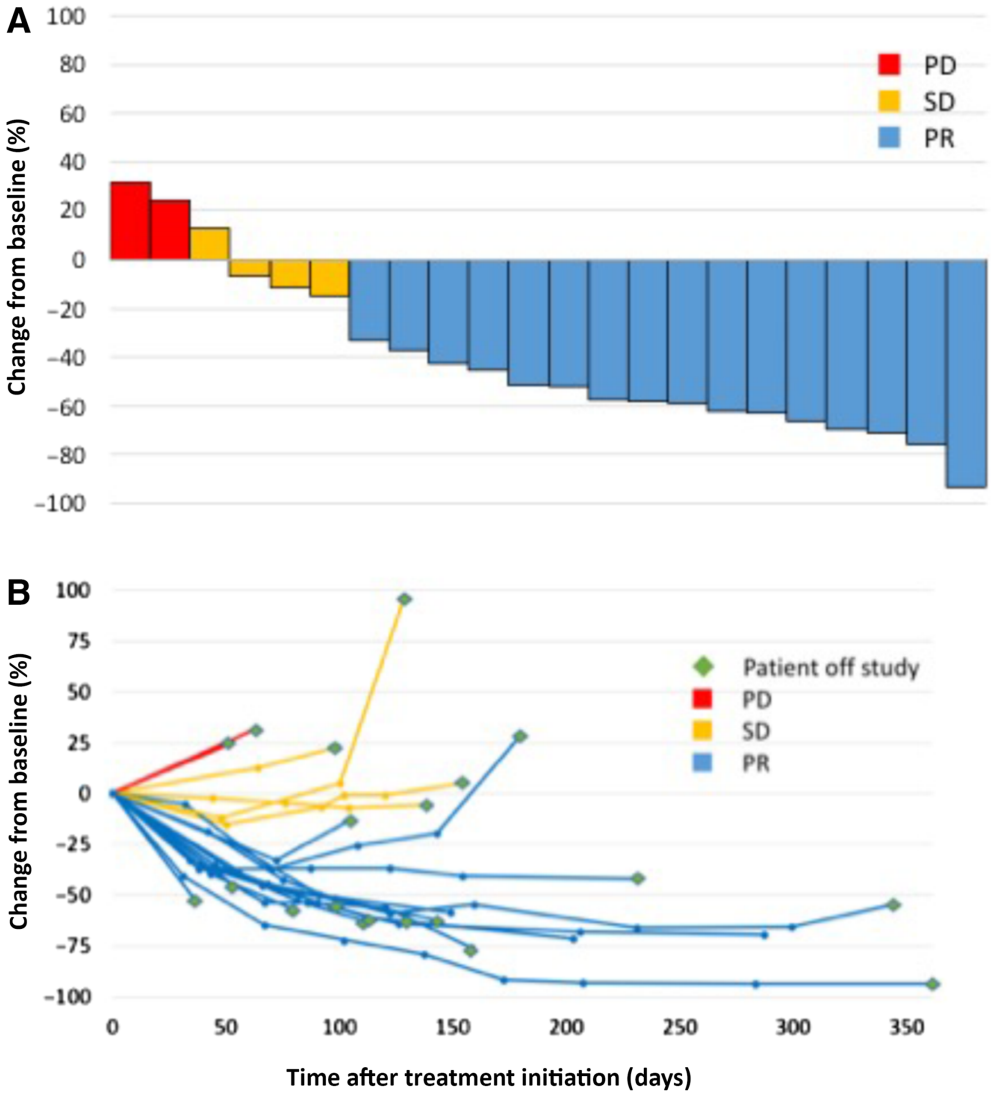

Figure 1. Tumor response. **(A):** Waterfall plot analysis of the maximum percentage change in target lesion size according to RECIST for 5-fluorouracil, docetaxel, and nedaplatin (UDON) therapy in 22 patients. **(B):** Spider plot analysis of the percentage change in target lesion size during UDON therapy in 22 patients.
Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

2-weekly DCF [4]. Spider plot analysis revealed a rapid response in 11 of the 16 patients showing a partial response (PR), with these individuals achieving tumor shrinkage of ≥30% after one cycle of UDON chemotherapy. The median PFS was 6.0 months (range, 0.9 months to not reached), and the median OS was 11.2 months (range, 4.0 months to not reached). The high antitumor efficacy of UDON was also reflected in survival, with a median PFS and OS of 6.0 and 11.2 months, respectively, values that are again similar to those for DCF [2], which has yielded a median PFS and OS of 5.8–7.0 months and 11.1–13.0 months, respectively.

The most frequent severe nonhematologic toxicities in the present study were lung infection and hyponatremia, each with an incidence of 13.0%, followed by mucosal inflammation with an incidence of 8.7%, and then anorexia, nausea, and fatigue with an incidence of 4.3%. For DCF regimens, the most frequent nonhematologic toxicities of grade ≥ 3 (nausea, anorexia, and hyponatremia) were observed in 10%–30% of patients [2]. The lower nonhematologic toxicity of UDON versus DCF is likely attributable to the substitution of nedaplatin for cisplatin, as suggested by a recent phase III study comparing concurrent chemoradiotherapy with nedaplatin versus that with cisplatin in patients with nasopharyngeal carcinoma of stage II–IVB, with the frequency of vomiting, nausea, and anorexia of grade 3 or 4 being significantly higher in the cisplatin arm [5]. Together, these data suggest that UDON is as effective as DCF and potentially less toxic in terms of nonhematologic events.

In summary, the UDON regimen was well tolerated and showed promising antitumor activity in terms of both objective response rate and survival for patients with advanced or recurrent esophageal squamous cell carcinoma in the first-line setting. The high response rate as well as the rapid and marked tumor shrinkage associated with UDON suggest that further evaluation of this regimen in the neoadjuvant setting is warranted.

Trial Information	
Disease	Esophageal cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Toxicity
Secondary Endpoint	Dysphagia score
Additional Details of Endpoints or Study Design	

The study was designed as a single-center and open-label phase II trial. The primary endpoint was RR, with secondary endpoints including PFS, OS, dysphagia score, and safety. Analysis of efficacy was performed with the full analysis set, which consists of all patients with the exception of those found to be ineligible after enrollment.

Tumor response and progression were assessed by investigators on the basis of RECIST (version 1.1) at baseline and every 4 weeks after treatment onset until disease progression. The RR and disease control rate were defined as the percentage of patients who achieved a confirmed complete response (CR) or PR or a confirmed CR, PR, or stable disease (SD), respectively. PFS was calculated as the time from the first day of treatment to the first day of documented progression or death. OS was calculated from the first day of treatment to death from any cause or the date of last contact. The probability of survival as a function of time was estimated with the Kaplan-Meier method. Dysphagia was evaluated at baseline and then immediately after each cycle of UDON therapy. The dysphagia score was determined as previously described according to the following scale: 0, able to consume a normal diet (no dysphagia); 1, able to swallow certain solid foods; 2, able to swallow only semisolid foods; 3, able to swallow liquids only; and 4, unable to swallow anything (total dysphagia). All patients were hospitalized for at least days 1–6 of each treatment cycle to allow for symptom evaluation and assessment of daily consumption of solid, semisolid, or liquid food.

Toxicity was graded according to National Cancer Institute Common Terminology Criteria version 4.0. Side effects were managed with standard supportive measures, and granulocyte colony-stimulating factor was administered if medically necessary. Tumor stage was classified according to the sixth edition of the tumor-node-metastasis classification system developed by the International Union Against Cancer. Computed tomography was performed every two cycles until the tumor progressed.

Investigator's Analysis	Active and should be pursued further

Drug Information	
Drug 1	
Generic/Working Name	Fluorouracil
Drug Type	Small molecule
Drug Class	Antimetabolite
Dose	800 mg/m^2
Route	Continuous intravenous infusion
Schedule of Administration	5-FU (800 mg/m^2 per day) was administered as a continuous intravenous infusion on days 1–5 every 4 weeks.
Drug 2	
Generic/Working Name	Nedaplatin
Dose	90 mg/m^2
Route	IV
Schedule of Administration	Nedaplatin (90 mg/m^2) was administered as a 90-minute intravenous infusion on day 1, every 4 weeks.
Drug 3	
Generic/Working Name	Docetaxel
Dose	35 mg/m^2
Route	IV
Schedule of Administration	Docetaxel (35 mg/m^2) was administered as an infusion on days 1 and 15, every 4 weeks.

Patient Characteristics	
Number of Patients, Male	20
Number of Patients, Female	3
Stage	
Disease status, *n* (%)	
Metastatic	18 (78.3)
Recurrent	5 (21.7)
T stage, *n* (%)	
T1a/T1b	0/2 (0/8.7)
T2	3 (13.0)
T3	14 (60.9)
T4a/T4b	0/4 (0/17.4)
N stage, *n* (%)	
N0	1 (4.3)
N1	4 (17.4)
N2	8 (34.8)
N3	10 (43.5)
M stage, *n* (%)	
M0	5 (21.7)
M1	18 (78.3)
Metastatic organs, *n* (%)	
Lymph nodes	22 (95.7)
Liver	5 (21.7)
Lung	3 (13.0)
Bone	3 (13.0)
Adrenal grand	1 (4.3)
Age	Median (range): 66 (48–79)
Number of Prior Systemic Therapies	None
Performance Status: ECOG	0 — 4
	1 — 18
	2 — 1
Serum creatinine, mg/dL, median (range)	0.81 (0.52–1.09)
Creatinine clearance[a], mL/minute, median (range)	75 (33–117)
Tumor histology: squamous cell carcinoma, *n* (%)	23 (100)
Tumor location, *n* (%)	
Cervical	0 (0)
Upper thoracic	3 (13.0)
Middle thoracic	11 (47.8)
Lower thoracic	9 (39.1)
Abdominal	0 (0)
Dysphagia score (baseline)	***n* (%)**
0 (asymptomatic)	8 (34.8)
1 (eat solid diet with some dysphagia)	9 (39.1)
2 (eat semisolid diet)	5 (21.7)
3 (drink liquid diet)	1 (4.3)
4 (complete dysphagia)	0 (0)
Cancer Types or Histologic Subtypes	Squamous cell carcinoma, 23

Primary Assessment Method	
Title	Efficacy analyses
Number of Patients Screened	23
Number of Patients Enrolled	23
Number of Patients Evaluable for Toxicity	23
Number of Patients Evaluated for Efficacy	22
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 16 (72.7)
Response Assessment SD	*n* = 4 (18.2)
Response Assessment PD	*n* = 2 (9.1)
Response Assessment OTHER	*n* = 0 (0%)
(Median) Duration Assessments PFS	6.0 months, CI: 0.9 to not reached
(Median) Duration Assessments OS	11.2 months, CI: 4.0 to not reached

Adverse Events					
Adverse event	**All grades, *n* (%)**	**Grade 1, *n* (%)**	**Grade 2, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**
Hematologic					
Leukopenia	21 (91.3)	1 (4.3)	11 (47.8)	9 (39.1)	0 (0)
Neutropenia	21 (91.3)	0 (0)	1 (4.3)	11 (47.8)	9 (39.1)
Anemia	23 (100)	6 (26.0)	11 (47.8)	6 (26.0)	0 (0)
Thrombocytopenia	15 (65.2)	11 (47.8)	2 (8.7)	0 (0)	2 (8.7)
Febrile neutropenia	2 (8.7)	—	—	2 (8.7)	0 (0)
Nonhematologic					
Anorexia	20 (87.0)	9 (39.1)	10 (43.5)	1 (4.3)	0 (0)
Constipation	16 (69.6)	2 (8.7)	14 (60.9)	0 (0)	0 (0)
Mucosal inflammation	16 (69.6)	2 (8.7)	12 (52.2)	2 (8.7)	0 (0)
Fatigue	11 (47.8)	7 (30.4)	3 (13.0)	1 (4.3)	—
Nausea	11 (47.8)	7 (30.4)	3 (13.0)	1 (4.3)	—
Vomiting	1 (4.3)	1 (4.3)	0 (0)	0 (0)	0 (0)
Diarrhea	9 (39.1)	5 (21.7)	4 (17.4)	0 (0)	0 (0)
Pyrexia	2 (8.7)	2 (8.7)	0 (0)	0 (0)	0 (0)
Alopecia	15 (65.2)	4 (17.4)	11 (47.8)	—	—
Peripheral sensory neuropathy	5 (21.7)	3 (12.0)	2 (8.7)	0 (0)	0 (0)
Lung infection	4 (17.4)	—	1 (4.3)	3 (13.0)	0 (0)
Elevated aspartate aminotransferase	11 (47.8)	8 (34.8)	2 (8.7)	1 (4.3)	0 (0)
Elevated alanine aminotransferase	8 (34.8)	7 (30.4)	1 (4.3)	0 (0)	0 (0)
Drug-induced interstitial pneumonia	3 (13.0)	1 (4.3)	2 (8.7)	0 (0)	0 (0)
Increased creatinine	5 (21.7)	2 (8.7)	3 (13.0)	0 (0)	0 (0)
Hyperkalemia	13 (56.5)	8 (34.8)	4 (17.4)	1 (4.3)	0 (0)
Hyponatremia	19 (82.6)	16 (69.6)	—	3 (13.0)	0 (0)
Hypercalcemia	2 (8.7)	1 (4.3)	0 (0)	0 (0)	1 (4.3)
Proteinuria	4 (17.4)	1 (4.3)	3 (13.0)	0 (0)	—
Esophagotracheal fistula	1 (4.3)	0 (0)	0 (0)	0 (0)	1 (4.3)
Esophagopulmonary fistula	1 (4.3)	0 (0)	0 (0)	1 (4.3)	0 (0)

Abbreviation: —, not defined in CTCAE version 4.0.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Esophageal cancer is the sixth leading cause of cancer deaths worldwide [6]. Surgery, radiation therapy, and chemotherapy are the major treatment modalities for esophageal cancer. However, the outcome for patients with metastatic esophageal cancer or with cancer recurrence after curative therapy is poor. In Japan, combination therapy with cisplatin plus 5-fluorouracil (5-FU) is recognized as a standard of care for medically fit patients with advanced or recurrent esophageal cancer, with such treatment yielding an overall response rate (RR) of 35% and median overall survival (OS) time of 5.3 or 9.2 months for nonresponders and responders, respectively [7, 8]. Given that most patients with advanced esophageal cancer manifest dysphagia, odynophagia, or dehydration [9], often resulting in a poor clinical condition and prognosis [10, 11], a chemotherapy regimen that can achieve a high response rate with low toxicity is desirable for such individuals.

A regimen consisting of 3- or 4-weekly docetaxel in addition to cisplatin and 5-FU (DCF) has been examined in an attempt to improve outcome for patients with metastatic esophageal cancer [12–15]. Although this regimen shows a substantial antitumor effect, with an RR of 35%–72%, it is also associated with severe toxicity, with febrile neutropenia, leukopenia, and anorexia of grade ≥ 3 being observed in 12%–21%, 9%–73%, and 16%–26% of patients, respectively. Given that this high incidence of toxicity was attributed to single-dose administration of docetaxel, weekly or biweekly divided administration of docetaxel in addition to cisplatin–5-FU (weekly or 2-weekly DCF) was evaluated and found to be associated with a markedly lower incidence of febrile neutropenia (0%–15%) [3, 4, 16, 17] compared with 3- or 4-weekly DCF as well as to yield an RR of 34%–62%.

Cisplatin treatment is associated with severe hematologic toxicities such as myelosuppression as well as nonhematologic toxicities including nephrotoxicity, nausea, and nephropathy, which can result in treatment disruption in patients with advanced esophageal cancer who are likely to be especially susceptible to such toxicities. On the other hand, the cisplatin analog nedaplatin (*cis*-diammine-glycolatoplatinum) has been shown to be potentially active against squamous cell carcinoma as well as to be less toxic than cisplatin [18–22]. We have therefore developed the triplet combination therapy of 5-FU, biweekly docetaxel, and nedaplatin (UDON). In a phase I study of UDON in patients with recurrent or metastatic esophageal cancer [1], no dose-limiting toxicity was observed at any level and the planned dose escalation was completed without reaching the maximum tolerated dose. No toxicity of grade ≥ 4 was observed. The observed hematologic toxicities of grade 3 included neutropenia (55.6 %) and leukopenia (33.3 %). None of the patients developed febrile neutropenia, and no nonhematologic toxicity of grade 3 was apparent. Despite the small size of the phase I trial (n = 9), the UDON regimen showed potential efficacy with an overall RR of 77.8% and a disease control rate of 100%, with two complete responses. The study set the recommended dose of UDON for a phase II study as 5-FU at 800 mg/m^2 on days 1–5, docetaxel at 35 mg/m^2 on days 1 and 15, and nedaplatin at 90 mg/m^2 on day 1 every 4 weeks.

For further evaluation of the safety and efficacy of UDON, we have now performed a phase II study in patients with untreated recurrent or metastatic esophageal cancer, which is the subject of this report. The activity of UDON was again observed, with an overall response rate of 72.7% (Fig. 1A and B), progression-free survival of 6 months, and an OS of 11.2 months (Fig. 2). This regimen compares favorably with the DCF regimen and with historical benchmarks above. Of note, the antitumor efficacy of UDON was not limited to the measurable metastatic site but was also apparent at the primary lesion, as revealed by an improvement in the dysphagia score in 11 (64.7%) patients after treatment onset, with 7 individuals becoming dysphagia free.

The change in dysphagia score was evaluated in the efficacy subset with the exception of the patients with recurrence (n = 5), who were free of dysphagia at baseline (Fig. 3A). Along with the decreased dysphagia score in 11 (64.7%) patients, there was an improvement in the endoscopic images (Fig. 3B), which remained unchanged in the remaining 6 (35.3%) patients. The median dysphagia score thus declined from 1.2 before treatment to a minimum of 0.5 after therapy onset.

This marked effect of UDON on the primary tumor is similar to that of palliative chemoradiotherapy, in which 72% of such treated patients with advanced esophageal cancer show an improvement in dysphagia score [23], suggesting that UDON may be a new alternative to palliative radiation or a metallic stent for patients with severe dysphagia. However, a marked response of the primary lesion to UDON resulted in the development of esophagotracheal fistula and consequent treatment discontinuation in one patient. Given that this patient harbored a T4 tumor, the indication for UDON should be restricted to esophageal cancer of T3 or less in future trials.

The current phase II study included more than a few patients with a low creatinine clearance of <60 mL/minute. However, the toxicity profile of UDON was similar to that seen in our previous phase I trial [1], with the most frequent adverse events being hematologic. The incidence of hematologic toxicities of grade 3 or 4 in the present study was similar to that of DCF regimens [3, 4, 15, 17]. The incidence of febrile neutropenia (8.7%) was also similar to that for weekly or 2-weekly DCF regimens (≤14.6%) [3, 4, 17]. Importantly, both cases of febrile neutropenia in the present study were grade 3 and were successfully treated with oral antibiotics without granulocyte colony-stimulating factor or hospitalization. These data suggest that UDON can be safely administered to patients with esophageal cancer, even those with mild renal dysfunction. However, caution should be exercised with regard to the development of hematologic toxicities when UDON is administered to patients

with symptoms, as is also the case for DCF regimens, although all hematologic toxicities in the present study were reversible and manageable by dose reduction or interruption.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures

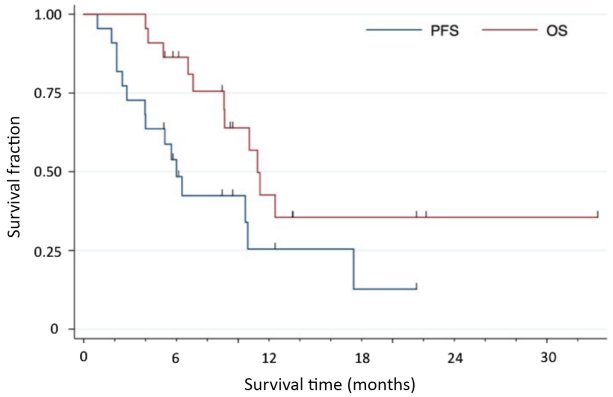

Figure 2. Kaplan–Meier analysis of PFS and OS for 22 study patients.

Abbreviations: OS, overall survival; PFS, progression-free survival.

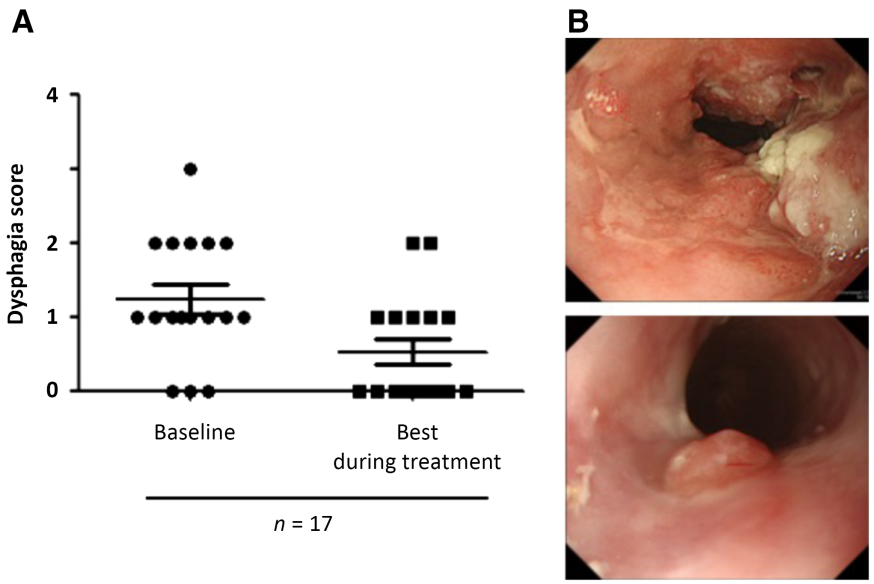

Figure 3. The marked effect of UDON on the primary tumor. Distribution of dysphagia score at baseline and the time of best improvement during treatment in 17 patients **(A)** as well as representative endoscopic images of the esophagus for 1 patient at baseline (top) and the time of best improvement in dysphagia score (bottom) during treatment **(B)**.