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Immediate Postoperative AbnobaVISCUM® F as an Adjuvant Treatment in Patients Receiving Standard Care after Pancreatic Cancer Resection

Seung Soo Hong[1,2], Munseok Choi[1,3], Seoung Yoon Rho[1,3], Sung Hyun Kim[1,2], Ho Kyoung Hwang[1,2], and Chang Moo Kang[1,2]

[1]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul;
[2]Pancreatobiliary Cancer Center, Yonsei Cancer Center, Severance Hospital, Seoul;
[3]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yongin Severance Hospital, Yongin, Korea.

Purpose: AbnobaVISCUM® F is an anti-malignant tumor agent derived from *Viscum album*, a mistletoe species parasitic to ash trees. It is known to exert anticancer effects by activating the patient's immune system without directly inducing tumor toxicity. We retrospectively investigated the anticancer effect of AbnobaVISCUM® F in patients with resected pancreatic cancer.

Materials and Methods: We reviewed a total of 985 patients who underwent radical resection for pancreatic cancer between January 2005 and August 2022 at Severance Hospital, Seoul, Korea. Patients were divided into two groups based on whether AbnobaVISCUM® F was administered (Viscum group) or not (Control group), and clinicopathologic characteristics, disease-free survival (DFS) and overall survival (OS) were compared after propensity score matching (PSM).

Results: Of the 985 patients, 310 received Viscum therapy at least 12 times (Viscum group), while 590 did not receive it at all (Control group). After PSM, both groups showed similar DFS (p=0.518), whereas the Viscum group showed superior OS (p<0.001). Subgroup analyses revealed better OS for the Viscum group in T1 (p=0.014), T2 (p=0.012), N0 (p=0.010), N1 (p=0.001), R0 resection patients (p<0.001), and in patients who underwent no adjuvant chemotherapy or chemotherapy regimens other than FOLFIRINOX (p<0.001). Multivariable analysis identified Viscum therapy as an independent factor for improved OS (hazard ratio 0.601, p< 0.001), although it did not significantly impact DFS.

Conclusion: Viscum treatment significantly improved OS in patients with completely resected stage I and II pancreatic cancer, particularly among those unable to tolerate adjuvant chemotherapy. This anticancer effect, based on immune enhancement, should be further investigated, and large-scale randomized controlled study is warranted.

Key Words: Viscum album, pancreatic cancer, adjuvant treatment

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies arising in the gastrointestinal tract, and survival rates have remained persistently low over the past two decades. Recent studies project that PDAC will become the third leading cause of cancer-related deaths by 2030.[1,2] Margin-negative radical resection is essential for potential cure; however, fewer than 20% of patients are deemed resectable at the time of diagnosis.[3] Even among those who undergo curative surgery, most experience recurrent cancer within 2 years, particularly in the liver, indicating that microscopic residual cancer cells may persist even after radical resection of PDAC. Therefore, postoperative adjuvant chemotherapy is considered the standard care for resected PDAC.[4]

It is hypothesized that patients with PDAC harbor the low-

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Corresponding author: Chang Moo Kang, MD, PhD, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: cmkang@yuhs.ac

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est volume of malignant cells in the immediate postoperative period. Theoretically, eliminating a small number of malignant cells may be more feasible than addressing a larger tumor burden, rendering this period optimal for anticancer treatment in resected PDAC. We refer to this as the "window period," during which chemotherapeutic agents are typically not administered, as this time is crucial for patient recovery; however, potential residual malignant cells may survive and proliferate due to postoperative inflammatory cytokines.

In clinical practice, anticancer treatment is typically deferred until full recovery from major surgery is achieved. Radical pancreatectomy is often associated with significant surgery-related morbidity and mortality, resulting in a transient state of immunocompromise.[5-8] Given the need for wound healing and full patient recovery following radical pancreatectomy, immediate postoperative adjuvant chemotherapy is often not practically feasible. The largest recent trial of adjuvant chemotherapy for pancreatic cancer demonstrated that early postoperative chemotherapy does not improve survival in patients with resected PDAC.[9]

What alternative treatment options could be considered? Ideal treatments administered during the window period should not adversely affect postoperative wound healing or compromise immune function, while still providing selective anticancer benefits.

Mistletoe (*Viscum album*) is a small plant that parasitizes a variety of host trees. Mistletoe has been reported to exert anticancer effects by stimulating the immune system without direct tumor toxicity.[10-12] Furthermore, mistletoe therapy is associated with minimal side effects, making it a potential candidate for administration during the window period in resected PDAC.[13-18] Currently, two types of mistletoe supplements are available: phytotherapeutic extracts and homeopathically produced preparations.[19]

In this study, we retrospectively reviewed our clinical experiences with immediate postoperative mistletoe therapy (AbnobaVISCUM® F, Viscum) during the window period following curative resection of PDAC and analyzed its long-term oncologic impact in patients with resected PDAC.

MATERIALS AND METHODS

We conducted a retrospective review of 985 patients who underwent radical resection for PDAC from January 2005 to August 2022 at Severance Hospital, Seoul, Korea. Patients were divided into two groups based on whether they received AbnobaVISCUM® F (Viscum group) or not (Control group). Clinicopathologic characteristics, disease-free survival (DFS), and overall survival (OS) were compared before and after propensity score matching (PSM). Survival data were followed up until August 2024. In subgroup analyses, we evaluated DFS and OS between the two groups based on adjuvant chemotherapy status, T and N stage, and margin-negative resection to identify appropriate candidates for Viscum therapy. Additionally, prognostic factors significantly affecting DFS and OS were analyzed using univariable and multivariable analyses.

There were no specific indications for the administration of Viscum. Potentially, all patients who underwent radical surgery for PDAC could be candidates for immediate postoperative Viscum therapy, with treatment decisions made at the surgeon's discretion and based on patient consent. In general, Viscum therapy is initiated on postoperative day 1 and discontinued before the start of adjuvant chemotherapy. The standard protocol involved administering Viscum F (0.02 mg/A) three times a week for 12 doses per month, with the total number of administrations ranging from one to 187, depending on the patient. In the Viscum group, only those who completed 12 or more administrations according to the standard protocol were included; those who received 11 or fewer administrations were excluded.

All statistical analyses were performed using the Statistical Package for the Social Sciences, version 28 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as means±standard deviations and were compared using independent t-tests, as the assumption of normality was considered satisfied based on the Central Limit Theorem due to the sufficiently large sample size. Categorical variables were compared using the chi-square test, and results are reported as numbers (n) and percentages (%). A 1:1 PSM analysis was conducted to minimize selection bias due to differences in comorbidities, tumor burden, staging, and length of hospital stay. The threshold for statistical significance was set at 0.05. To evaluate risk factors affecting DFS and OS, a Cox proportional hazards model was used, including variables with a $p<0.05$ in the univariable analysis for inclusion in the multivariable model.

This study was approved by the Institutional Review Board of Yonsei University College of Medicine (4-2021-0073).

RESULTS

Patients' general characteristics

Among the 985 patients who underwent radical resection for PDAC, 395 received at least one administration of Viscum therapy, with a median of 22 injections (range: 1–187) and a mean of 25.8±21.7 injections. Of these, 85 patients who received fewer than 12 administrations were excluded, and the remaining 310 patients (31.4%) who completed at least 12 administrations were included in the Viscum group. The Control group comprised 590 patients who did not receive any Viscum. We compared the demographic, clinical, and oncologic characteristics of the Control and Viscum groups (Table 1). Demographic characteristics, including age, sex, and BMI, did not differ significantly between the two groups; however, the Viscum group exhibited more advanced comorbidities [American Society of Anesthesiologists (ASA) scores, $p<0.001$] and lower preopera-

Table 1. Clinicopathologic Characteristics of Control and Viscum Groups

	Control group (n=590)	Viscum group (n=310)	*p*
Age (yr)	63.3±9.4	63.9±10.0	0.386
Sex (male)	337 (57.1)	151 (48.7)	0.016
BMI (kg/m^2)	23.1±2.9	23.1±3.3	0.875
ASA score			<0.001*
1	91 (15.4)	16 (5.2)	
2	278 (47.1)	115 (37.1)	
3	219 (37.1)	179 (57.7)	
4	2 (0.3)	0 (0.0)	
Preop. CA 19-9 (U/mL)	308.9±1091.0	141.0±424.9	0.001*
Operation			0.674
PD	355 (60.2)	191 (61.6)	
DP	235 (39.8)	119 (38.4)	
Hospital stay (day)	20.2±19.6	14.1±21.5	<0.001*
Neoadjuvant CTx	168 (28.5)	159 (51.3)	<0.001*
Adjuvant CTx	453 (76.8)	265 (85.5)	0.002*
Regimen			<0.001*
FOLFIRINOX	39 (19.7)	159 (51.3)	
Gemcitabine-based	324 (54.9)	94 (30.3)	
Other regimen	90 (15.3)	12 (3.9)	
Tumor size (cm)	2.6±1.5	2.3±1.2	<0.001*
T stage (AJCC 8th)			0.022*
T1	196 (33.2)	128 (41.3)	
T2	336 (56.9)	163 (52.6)	
T3	58 (9.8)	19 (6.1)	
N stage (AJCC 8th)			0.021*
N0	274 (46.4)	165 (53.2)	
N1	222 (37.6)	115 (37.1)	
N2	94 (15.9)	30 (9.7)	
Retrieved LN (n)	17.5±11.2	16.9±10.8	0.441
Positive LN (n)	1.6±2.4	1.2±2.0	0.010*
Differentiation			0.079
Well	65 (11.0)	38 (12.3)	
Moderate	392 (66.4)	198 (63.9)	
Poor	78 (13.2)	48 (15.5)	
Etc.	3 (0.5)	7 (2.3)	
LVI (+)	209 (35.4)	100 (32.3)	<0.001*
PNI (+)	407 (69.0)	231 (74.5)	<0.001*
Margin (+)	101 (17.1)	60 (19.4)	0.406

BMI, body mass index; ASA, American Society of Anesthesiologists; Preop., preoperative; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; CTx, chemotherapy; AJCC, American Joint Committee on Cancer; LN, lymph node; LVI, lymphovascular invasion; PNI, perineural invasion.
Data are presented as mean±standard deviation or n (%).
*p<0.05.

tive tumor marker levels (CA19-9: Control group 308.9±1091.0 vs. Viscum group 141.0±424.9, p=0.001).

Overall comparative analysis between Viscum group and Control group

Postoperative findings showed no significant difference in the types of operations performed between the two groups (p=0.674). However, the Viscum group demonstrated a shorter hospital stay (Control group 20.2±19.6 days vs. Viscum group 14.1±21.5 days, p<0.001) and a higher percentage of patients receiving neoadjuvant chemotherapy (Control group 28.5% vs. Viscum group 51.3%, p<0.001) and adjuvant chemotherapy (Control group 76.8% vs. Viscum group 85.5%, p=0.002). Regarding adjuvant chemotherapy regimens, more than half of the Viscum group received FOLFIRINOX-based chemotherapy, while most of the Control group received gemcitabine-based chemotherapy (p<0.001). Pathological findings indicated a more advanced stage of pancreatic cancer in the Control group, with more advanced T (p=0.022) and N stages (p=0.021), and a higher number of metastatic lymph nodes (Control group 1.6±2.4 vs. Viscum group 1.2±2.0, p=0.010). The rates of lymphovascular invasion (LVI) and perineural invasion (PNI) were similar between the two groups, yet still reached statistically significance. No significant differences were noted in the retrieved number of lymph nodes, differentiation, or margin status between the two groups.

In survival analysis, the Viscum group demonstrated superior outcomes in both DFS (2-year DFS: Control group 29.8% vs. Viscum group 37.3%, p=0.047) and OS (2-year OS: Control group 53.5% vs. Viscum group 74.7%, p<0.001) compared to the Control group (Fig. 1).

Propensity score-matched comparative analysis between Viscum and Control groups; Viscum group showed superior OS in resected pancreatic cancer

We conducted PSM using covariates including CA 19-9, tumor size, number of positive lymph nodes, ASA score, hospital stay, chemotherapy regimen, LVI, and PNI, with a caliper of 0.05. After PSM, the demographic, clinical, and oncologic characteristics of the Control (n=190) and Viscum groups (n=190) did not show significant differences (Table 2). Moreover, the majority of standardized mean difference values were below 0.1, suggesting that covariate balance between the groups was generally well achieved. Using the propensity score matched data, we further analyzed survival in both groups and performed subgroup analysis. Fig. 2 shows the survival curve for the Control and Viscum groups after PSM. The previously observed superior DFS in the Viscum group was no longer significant after PSM (2-year DFS: Control group 32.6% vs. Viscum group 31.5%; p=0.518); however, the OS remained significantly better in the Viscum group (2-year OS: Control group 54.6% vs. Viscum group 70.1%; p<0.001).

In subgroup analysis, we compared survival between the two groups based on the administration of FOLFIRINOX chemotherapy, T and N stage, and resection margin status. For patients who did not receive adjuvant chemotherapy or received chemotherapy with gemcitabine or other regimens (n=304), the Viscum group (n=151) exhibited superior OS compared to the Control group (n=153) (2-year OS: Control group 51.6% vs.

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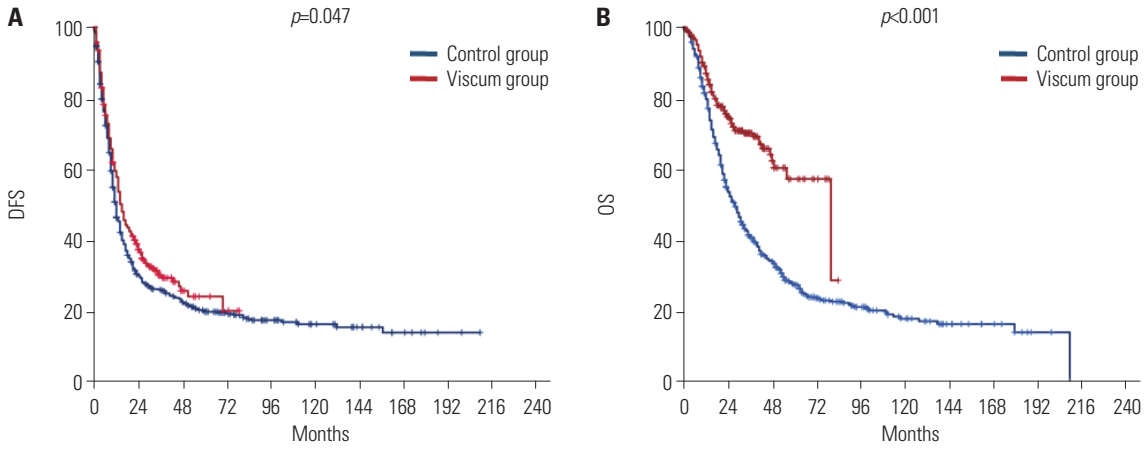

Fig. 1. Survival analysis of Control and Viscum groups. (A) The Viscum group demonstrated superior outcomes in both DFS (2-year DFS: Control group, 29.8% vs. Viscum group, 37.3%, p=0.047). (B) OS (2-year OS: Control group, 53.5% vs. Viscum group, 74.7%, p<0.001) compared to the Control group. DFS, disease-free survival; OS, overall survival.

Viscum group 67.9%, p<0.001), without a difference in DFS (2-year DFS: Control group 32.0% vs. Viscum group 28.8%, p=0.405). However, among patients who received adjuvant FOLFIRINOX chemotherapy (n=75), there were no survival differences between the two groups: Control group (n=36, 2-year DFS 35.1%) vs. Viscum group (n=39, 2-year DFS 41.0%, p=0.884) and OS (Control group 67.2% vs. Viscum group 78.0%, p=0.175) (Fig. 3).

Propensity score-matched comparative analysis between Viscum and Control groups; Viscum group showed superior OS in margin-negative early pancreatic cancer

The summary of subgroup analyses according to T stage, N stage, and margin status is presented in Table 3. For the analysis by T stage, the Viscum group demonstrated superior OS in T1 (p=0.014) and T2 (p=0.012) stages, while there was no OS difference in T3 stage between the two groups. DFS did not differ significantly across all T stages.

Similarly, the Viscum group exhibited superior OS in N0 (p=0.010) and N1 (p=0.001) stages without differences in DFS. However, in the N2 group, the Viscum group showed worse DFS (p=0.023) compared to the Control group.

For patients with a pathological report indicating R0 resection, the Viscum group had better OS (p<0.001); however, in patients with R1 resection, the Viscum group exhibited significantly worse DFS (p=0.050).

Determining prognostic factor in resected pancreatic cancer

We performed univariable and multivariable analyses to identify factors associated with DFS and OS. In univariable analysis affecting DFS, preoperative CA 19-9 (HR 1.000, p<0.001), T stage (p<0.001), N stage (p<0.001), poorly differentiated pathology [hazard ratio (HR) 1.614, p=0.045], LVI+ (HR 1.541, p<0.001), and PNI+ (HR 1.681, p<0.001) were found to be independent factors. In the multivariable analysis for DFS, T stage (p=0.030) and N stage (p<0.001) remained independent predictors of recurrence. Neither Viscum therapy (p=0.528) nor the number of Viscum administrations (p=0.053) was associated with DFS.

Regarding OS, preoperative CA 19-9 (p<0.001), adjuvant FOLFIRINOX chemotherapy (HR 0.543, p=0.005), T stage (p=0.015), N stage (p<0.001), LVI+ (HR 1.880, p<0.001), PNI+ (HR 1.491, p=0.024), margin+ (HR 1.487, p=0.015), Viscum therapy (HR 0.577, p<0.001) and the number of Viscum administration (HR 0.990, p=0.031) were identified as independent factors in univariable analysis. In the multivariable analysis for OS, preoperative CA 19-9 (HR 1.000, p=0.018), adjuvant FOLFIRINOX chemotherapy (HR 0.429, p<0.001), N stage (p=0.003), LVI+ (HR 1.577, p=0.005), and Viscum therapy (HR 0.601, p<0.001) remained independent prognostic factors. However, the number of Viscum administrations was not associated with OS (p=0.983) (Table 4).

DISCUSSION

Mistletoe has been utilized as a complementary anticancer therapy for over a century. In 1902, Rudolf Steiner introduced *Viscum album* L. as an anticancer treatment regimen, with its main components, lectins and viscotoxins, believed to possess anticancer properties.[20,21] Mistletoe is recognized for enhancing patients' quality of life and exhibiting anticancer effects through apoptosis induction, angiogenesis inhibition, cell-cycle arrest, and immunomodulation.[22-25]

Despite numerous studies demonstrating the potential anticancer activity of mistletoe, gaps still exist in evidence supporting its roles in clinical oncology. In 2003, Ernst, et al.[26] conducted a narrative systematic review of randomized clinical trials, concluding that current randomized controlled trials (RCTs) on mistletoe extracts showed insufficient evidence of oncologic benefits for cancer patients. Recently, Freuding, et al.[27] conducted a systematic review on the potential role of mistletoe in cancer treatment by analyzing 28 published RCTs involving 2639

patients. They found that mistletoe did not consistently demonstrate survival advantages across most studies. However, for specific cancers, including breast cancer, colorectal cancer, advanced glioma, non-metastatic uterine cancer, and pancreatic cancer, mistletoe showed improved survival, warranting further investigation.

Table 2. Clinicopathologic Characteristics of Control and Viscum Groups after 1:1 Propensity Score Matching

	Control group (n=190)	Viscum group (n=190)	*p*	SMD
Age (yr)	63.4±8.4	65.6±9.5	0.056	0.245
Sex (male)	109 (57.4)	96 (50.5)	0.181	0.139
BMI (kg/m^2)	23.6±3.0	23.1±3.5	0.155	0.153
ASA score			0.461	
1	11 (5.8)	15 (7.9)		0.083
2	81(42.6)	63 (33.2)		0.194
3	97 (51.1)	112 (58.9)		0.157
4	1 (0.5)	0 (0.0)		0.142
Preop. CA 19-9 (U/mL)	176.3±341.1	179.9±521.1	0.937	0.008
Operation			0.530	
PD	117 (61.6)	111 (58.4)		0.065
DP	73 (38.4)	79 (41.6)		0.065
Hospital stay	17.0±8.5	15.3±27.2		0.403
Neoadjuvant CTx	79 (41.6)	78 (41.1)	0.917	0.010
Adjuvant CTx	154 (81.1)	145 (76.3)	0.260	0.117
Regimen			0.070	
FOLFIRINOX	37 (19.5)	39 (20.5)		0.025
Gemcitabine-based	90 (47.4)	94 (49.5)		0.042
Other regimen	27 (14.2)	12 (6.3)		0.265
Not done	36 (18.9)	45 (23.7)		0.117
Tumor size (cm)	2.3±1.2	2.5±1.4	0.434	0.153
T stage (AJCC 8th)			0.595	
T1	82 (43.2)	76 (40.0)		0.065
T2	95 (50.0)	96 (50.5)		0.010
T3	13 (6.8)	18 (9.5)		0.099
N stage (AJCC 8th)			0.643	
N0	94 (49.5)	102 (53.7)		0.084
N1	68 (35.8)	65 (34.2)		0.034
N2	28 (14.7)	23 (12.1)		0.076
Retrieved LN (n)	18.3±11.7	16.5±10.7	0.128	0.161
Positive LN (n)	1.3±1.8	1.3±2.2	0.980	0.000
Differentiation			0.679	
Well	24 (12.6)	23 (12.1)		0.015
Moderate	126 (66.3)	120 (63.2)		0.065
Poor	26 (13.7)	28 (14.7)		0.029
Etc.	1 (0.5)	4 (2.1)		0.149
LVI (+)	58 (30.5)	63 (33.2)	0.858	0.058
PNI (+)	146 (76.8)	144 (75.8)	0.970	0.024
Margin (+)	43 (22.6)	31 (16.3)	0.120	0.160

SMD, standardized mean difference; BMI, body mass index; ASA, American Society of Anesthesiologists; Preop., preoperative; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; CTx, chemotherapy; AJCC, American Joint Committee on Cancer; LN, lymph node; LVI, lymphovascular invasion; PNI, perineural invasion.
Data are presented as mean±standard deviation or n (%).

In particular, with regard to pancreatic cancer, Schad, et al.[28] retrospectively reviewed their experiences with intratumoral mistletoe therapy in unresectable pancreatic cancer patients. Patients undergoing mistletoe therapy exhibited a median survival ranging from 8.3 to 11 months, indicating the feasibility and safety of intratumoral mistletoe application, although oncologic effectiveness needs validation through RCTs. Tröger, et al.[29] conducted an RCT analyzing *Viscum album* extract's effects on OS in advanced metastatic pancreatic cancer patients. Their analysis demonstrated that *Viscum album* therapy yielded superior median survival compared to the Control group (4.8 months vs. 2.7 months, HR=0.49, $p<0.001$) without adverse drug events. Additionally, mistletoe treatment significantly improved the quality of life in locally advanced or metastatic pancreatic cancer patients, as evidenced by changes in body weight during the trial. This study suggests positive oncologic effects of mistletoe on pancreatic cancer, although it focused on late-stage disease.

For long-term survival in pancreatic cancer, curative resection with negative resection margins is crucial. To the best of our knowledge, this study is the first to evaluate the oncologic role of mistletoe therapy in resected pancreatic cancer using the "window period" concept. Furthermore, we analyzed recurrence and survival rates from a series of 900 cases of resected pancreatic cancer over 18 years, which encompasses the largest number of cases among retrospective studies reported to date, thereby increasing statistical power. We sought to minimize confounding factors by including only patients who received at least 12 administrations of Viscum. Although the Viscum group showed superior recurrence and survival outcomes compared to the Control group, interpretation of these results is limited by the significant disparity in tumor burden between the two groups. Notably, Viscum therapy was primarily introduced after 2015 in our institution; consequently, the Viscum group included more recently operated patients. Concurrently, the institution adopted FOLFIRINOX neoadjuvant chemotherapy around the same time, contributing to overall tumor downstaging. These factors may explain the superior survival rate observed in the Viscum group.

To address these challenges, we performed PSM with a caliper of 0.05 to mitigate confounding factors, ensuring that only comparable cases were matched, albeit with some loss of cases. This effort resulted in the elimination of clinicopathological differences between the two groups, and subsequent survival analysis revealed that the Viscum group improved OS within the matched patient cohort. In subgroup analyses aimed at identifying patients who might benefit from Viscum therapy, we found that the Viscum group demonstrated improved OS without a difference in DFS only in patients who did not receive adjuvant chemotherapy or who received regimens other than FOLFIRINOX. Conversely, the potent triple cytotoxic effects of FOLFIRI-

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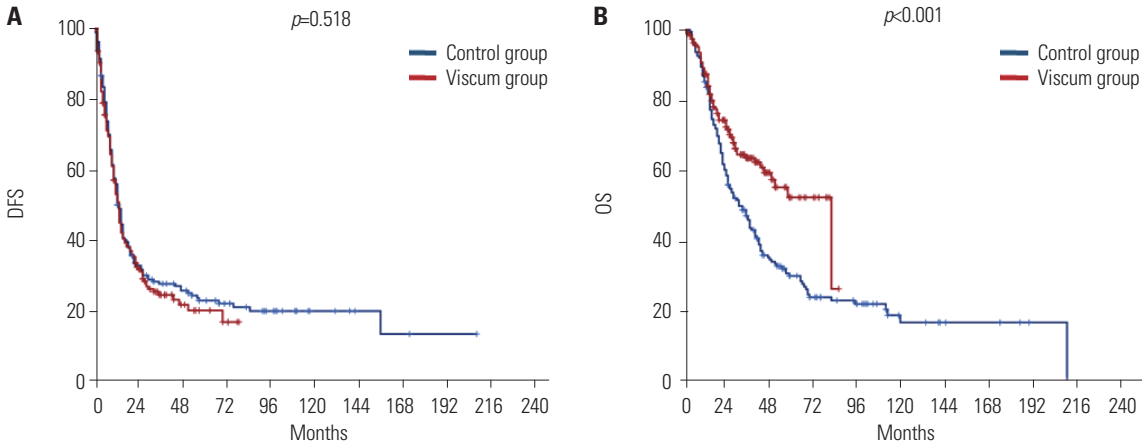

Fig. 2. Survival analysis of control and viscum groups after PSM. (A) The superior DFS of the Viscum group diminished after PSM (2-year DFS: Control group, 32.6% vs. Viscum group, 31.5%; p=0.518). (B) However, the OS in the Viscum group remained superior even after PSM (2-year OS: Control group, 54.6% vs. Viscum group, 70.1%; p<0.001). PSM, propensity score matching; DFS, disease-free survival; OS, overall survival.

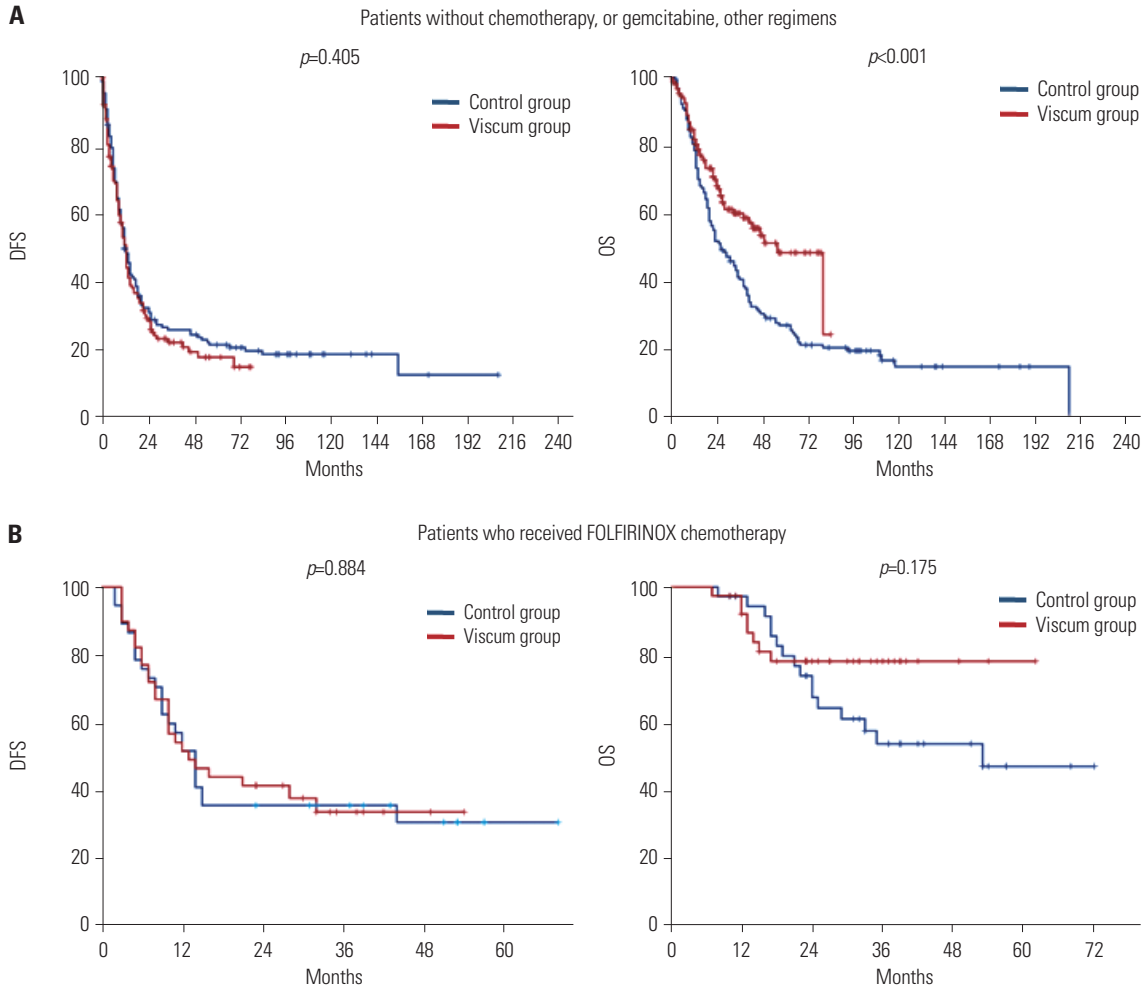

Fig. 3. Subgroup survival analysis according to the chemotherapy regimen. (A) For patients who did not receive adjuvant chemotherapy or received chemotherapy with gemcitabine or other regimens (n=304), the Viscum group (n=151) exhibited superior OS compared to the Control group (n=153) (2-year OS: Control group, 51.6% vs. Viscum group, 67.9%; p<0.001), without a difference in DFS (2-year DFS: Control group, 32.0% vs. Viscum group, 28.8%; p=0.405). (B) However, among patients who received adjuvant FOLFIRINOX chemotherapy (n=75), there were no survival differences between the two groups: Control group (n=36; 2-year DFS, 35.1%) vs. Viscum group (n=39; 2-year DFS, 41.0%; p=0.884) and OS (Control group, 67.2% vs. Viscum group, 78.0%; p=0.175). DFS, disease-free survival; OS, overall survival.

NOX may have masked the benefits of Viscum in patients who received it. Although not statistically significant, a difference in mean and median survival was observed even in the adjuvant FOLFIRINOX group, suggesting that the effect of Viscum treatment warrants further evaluation as case numbers increase.

Table 3. Subgroup Analysis of OS and DFS According to T Stage, N Stage, and Resection Margin Status

	2-year DFS		*p*	2-year OS		*p*
	Control	Viscum		Control	Viscum	
T stage						
T1	43.8	44.5	0.972	62.2	80.0	0.014*
T2	23.0	23.5	0.614	50.6	63.8	0.012*
T3	30.8	13.8	0.388	34.6	60.3	0.209
N stage						
N0	45.4	45.4	0.730	64.5	79.5	0.010*
N1	20.9	18.8	0.273	47.0	71.1	0.001*
N2	17.6	4.6	0.023*	39.0	26.6	0.268
R0 resection						
R0	31.9	34.0	0.943	55.2	76.2	<0.001*
R1	34.9	18.1	0.050*	52.1	38.3	0.360

DFS, disease-free survival; OS, overall survival.
*p<0.05.

The observed discrepancy between comparable DFS and improved OS in the Viscum-treated group suggests that Viscum therapy may exert benefits beyond tumor recurrence control. One potential mechanism is its immunomodulatory effect, which may enhance systemic immune surveillance, reduce cancer-related inflammation, and improve the host's resilience against disease progression or treatment-related complications. Furthermore, Viscum has been reported to improve quality of life and reduce chemotherapy-associated toxicity, which could indirectly contribute to prolonged survival. These findings suggest that Viscum may not necessarily prevent recurrence, but instead promote a more favorable physiological environment that supports long-term survival, even after recurrence occurs.

Although Viscum therapy has been associated with improved immune modulation and potential survival benefits in various cancers, our subgroup analysis revealed a paradoxical finding: patients with stage N2 pancreatic cancer who received Viscum showed worse DFS compared to those who did not. This unexpected outcome may be due to residual confounding despite PSM, particularly if Viscum was preferentially administered to patients perceived to have more aggressive disease or a poorer prognosis. Additionally, the immunologic burden and tumor microenvironment in advanced nodal disease may limit the

Table 4. Univariable and Multivariable Analyses of Factors Affecting DFS and OS

Survival factors	DFS				OS			
	Univariable		Multivariable		Univariable		Multivariable	
	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Preop. CA 19-9	1.000	<0.001*	1.000	0.066	1.000	<0.001*	1.000	0.018*
Neoadjuvant CTx	1.256	0.060			1.234	0.135		
FFX adjuvant CTx	0.798	0.149			0.543	0.005*	0.429	<0.001*
T stage		<0.001*		0.030*		0.015*		0.746
T1	ref		ref		ref		Ref	
T2	1.759	<0.001*	1.365	0.029*	1.516	0.005*	1.136	0.454
T3	2.072	0.001*	1.701	0.025*	1.513	0.133	1.147	0.652
N stage		<0.001*		<0.001*		<0.001*		0.003*
N0	ref		ref		ref		Ref	
N1	1.764	<0.001*	1.515	0.003*	1.552	0.005*	1.447	0.027*
N2	2.601	<0.001*	2.069	<0.001*	2.759	<0.001*	2.094	<0.001*
Differentiation		0.119				0.285		
Well	ref				ref			
Moderate	1.220	0.306			1.180	0.454		
Poor	1.614	0.045*			1.619	0.077		
Undiff.	0.479	0.313			0.685	0.608		
Not reported	0.964	0.900			0.936	0.851		
LVI (+)	1.541	<0.001*	1.068	0.640	1.880	<0.001*	1.577	0.005*
PNI (+)	1.681	<0.001*	1.289	0.126	1.491	0.024*	1.168	0.392
Margin (+)	1.188	0.242			1.487	0.015*	1.171	0.368
Viscum	1.079	0.528			0.577	<0.001*	0.601	<0.001*
No. of viscum	1.005	0.053			0.990	0.031*	1.000	0.983

DFS, disease-free survival; OS, overall survival; Preop., preoperative; CTx, chemotherapy; FFX, FOLFIRINOX; Undiff., undifferentiated; LVI, lymphovascular invasion; PNI, perineural invasion; No. of viscum, number of viscum administration.
*p<0.05.

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therapeutic efficacy of Viscum. Further prospective studies are warranted to clarify these interactions and determine whether Viscum's effect differs by disease burden or immune status.

In summary, the significant OS advantage observed in the Viscum group for T1, T2, N0, N1, and R0 resection patients, contrasted with poorer DFS observed in patients with advanced disease (N2 and R1 resection), suggests that Viscum may be particularly effective in completely resected stage I and II cancers, especially in patients unable to tolerate adjuvant chemotherapy due to poor general condition.

This study has several limitations, including its retrospective design, single-institution setting, and the heterogeneous number of Viscum administrations among patients, all of which could have influenced the outcomes. However, by applying currently available scientific approaches to minimize bias, we were able to confirm the nutraceutical significance of Viscum as part of the standard treatment for pancreatic cancer. According to our experience, Viscum has few side effects and can be readily applied in clinical practice.

In conclusion, this study demonstrated the feasibility, safety, and oncologic benefits of short-term postoperative Viscum therapy in patients with resected pancreatic cancer. These findings underscore the need for further prospective research to evaluate the effects of Viscum therapy during the postoperative window as an adjunct treatment for resected early-stage pancreatic cancer.

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AUTHOR CONTRIBUTIONS

Conceptualization: Chang Moo Kang and Seung Soo Hong. Data curation: Seung Soo Hong, Munseok Choi, Seoung Yoon Rho, Sung Hyun Kim, and Ho Kyoung Hwang. Formal analysis: Seung Soo Hong. Funding acquisition: Chang Moo Kang. Investigation: Seung Soo Hong. Methodology: Seung Soo Hong. Project administration: Chang Moo Kang. Resources: Seung Soo Hong. Software: Seung Soo Hong. Supervision: Chang Moo Kang. Validation: Chang Moo Kang. Visualization: Seung Soo Hong. Writing—original draft: Seung Soo Hong and Chang Moo Kang. Writing—review & editing: Seung Soo Hong and Chang Moo Kang. Approval of final manuscript: all authors.

ORCID iDs

Seung Soo Hong https://orcid.org/0000-0001-9913-8437
Munseok Choi https://orcid.org/0000-0002-9844-4747
Seoung Yoon Rho https://orcid.org/0000-0002-1265-826X
Sung Hyun Kim https://orcid.org/0000-0001-7683-9687
Ho Kyoung Hwang https://orcid.org/0000-0003-4064-7776
Chang Moo Kang https://orcid.org/0000-0002-5382-4658

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