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Long-Term Experience of Craniopharyngioma Treatment in Single University-Based Hospital

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Case Report

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Abstract

Purpose

Craniopharyngioma is a relatively rare disease. Multimodality of treatment is still a challenge due to recurrence and treatment-related toxicities. While long-term treatment data in Thailand is still limited, this study aims to report 30 years of experience in craniopharyngioma treatment in a single institute.

Methods

Retrospective study includes all patients diagnosed with craniopharyngioma between January 1990 and January 2020. Demographic data and treatment outcomes were collected and analyzed.

Results

Ninety-eight patients were included in the analysis with a median age at diagnosis of 20.5 years (1–67 years). The majority of patients received surgical resection (98%). However, only 13.3% achieved gross total resection, and 8.2% received postoperative radiotherapy. With a median follow-up interval of 8.5 years (1–33 years), a 5-year progression-free survival rate was 39.3%. The median time to progression was 2.4 years. Whereas adjuvant radiotherapy was the only factor shown to be beneficial (HR 0.21, 95% CI 0.05–0.22, p = 0.03), Intra-cystic chemotherapy without any resection resulted in a detrimental outcome (HR 70.12, 95% CI 9.67-508.14, p = 0.03). However, overall survival rates remained high, 100% at 5 years. Radiotherapy still showed a favorable outcome at any course of the treatment. Five-year radiotherapy failure-free survival (RT-FFS) rate was 81.4%. Late endocrine dysfunction, especially hypothyroidism (96%), and delayed puberty (77.8%), obesity (69.2%), and visual field defect (43.1%) were common.

Conclusion

The multimodality treatment in craniopharyngioma has yielded promising survival rates, but disease progression is still challenging. Radiotherapy is effective in tumor control in both adjuvant and salvage settings. However, long-term toxicities should be carefully considered.

Introduction

Craniopharyngioma is a globally challenging condition, with new cases ranging from 0.5 to 2.5 per 1 million people per year. It typically manifests in individuals aged 5–15 and 45–60. [1, 2] According to the benign nature of the disease, long-term survival can be achieved after treatment. Typically, symptom manifestation depends on nearby organs, such as visual field impairment from optic pathway

compression or hormonal dysfunction due to pituitary gland or hypothalamus compression. These symptoms may be persistent and affect the quality of life after treatment.

Currently, various treatment modalities exist, including complete tumor resection, radiotherapy after partial surgical resection or after recurrence, and intra-cystic interferon injection, a procedure where interferon is directly injected into the cystic part of the tumor. While overall survival (OS) rates were consistent and remain high in many historical studies, progression-free survival (PFS) rates varied between treatment approaches. Whereas International studies indicated an OS rate of 80–90% for patients after gross total tumor removal, [3–5] partial tumor removal provides a worse outcome with a PFS rate of 30–40%. [3–7] However, additional radiotherapy after incomplete resection could lead to a PFS rate approaching 70–90%. [3, 4, 8–10] Lastly, Intra-cystic interferon injection was used to treat the cystic part of craniopharyngioma in many centers, but the efficacy remains inconclusive. [11]

Concerning long-term survival, every treatment method may cause long-term adverse events. The extension of surgery has a very high impact. Gross total tumor removal (GTR) may lead to hormonal abnormalities of approximately 60–70% and visual impairment of 30–40%. [3–7] Even reduced extension of surgery to subtotal resection (STR) followed by adjuvant radiotherapy still resulted in hormone deficiency and visual problems of almost 20–30%. [3–7] Furthermore, a study by Schoenfeld, et al. identified post-treatment cerebrovascular events in 3 out of 122 craniopharyngioma patients. [3] While intra-cystic interferon seems less invasive than surgical resection, headaches and fatigue can occur approximately 10–20% after treatment. [11]

In Thailand, there was limited long-term research on treatment outcomes for craniopharyngioma. This study aims to investigate the long-term effects of treatment, encompassing PFS, OS, local disease control (LC), and post-treatment side effects, focusing on hormonal abnormalities, cerebrovascular events, abnormal vision, and secondary brain tumors in a single medical university hospital in Thailand.

Material and method

Patient enrollment

All patients diagnosed with craniopharyngioma between January 1990 and January 2020 by pathological or clinical diagnosis through imaging were included in this retrospective study. Patients with a history of cranial irradiation or diagnosed with other primary brain malignancies either prior to or at the time of craniopharyngioma were all excluded. All clinical data were gathered according to the protocol approved by the local ethics committee (MURA2023/340) by the primary investigator until 31st December 2023, including demographic, treatment, imaging, survival, and toxicities data. A diagnostic neuroradiologist reviewed magnetic resonance imaging (MRI) of the brain of all patients to characterize baseline tumor and post-treatment tumor status.

Statistical analysis

The analysis was performed using Stata Standard Edition version 17.0. PFS was analyzed as a primary outcome, defined as the time from the date of the first treatment to the date of the documented progression after the first course of treatment, death from any cause, or any consequential event preceding the first salvage treatment, as recorded in the medical record or through radiographic evidence. Secondary outcomes were concentrated on OS, LC, and toxicity rates. Furthermore, this study also analyzed and reported both second progression-free survival (PFS2), defined as the time from the date of the second treatment to the date of the documented progression after salvage treatment, death from any cause, or any consequential event preceding the second salvage treatment, and radiotherapy failure-free survival (RT-FFS), defined by time from the date of completed radiotherapy to date of first documented progression after radiotherapy, death from any cause, or any consequential event proceeding to subsequent salvage treatment. Both outcomes could display the effectiveness of salvage treatment and radiotherapy.

Survival functions were computed utilizing the Kaplan-Meier method, and comparisons between the two arms were made through a log-rank test. The prognostic capability of the factors was assessed using the Cox proportional hazards regression model, encompassing both univariable and multivariable analyses.

Regarding toxicities, data on both endocrine disorders and impairment of visual acuity were recorded by adhering to CTCAE version 5.0. The abnormal endocrine function focused on grade 2 or more adverse events, which medical supplementation was necessary for the patients. We also gathered information on the visual field before and after treatment, as well as the latest investigation. Additionally, cerebrovascular events and any new brain tumors were reviewed from medical documents and collected after completion of the treatment up to the last follow-up. Moreover, we compiled information on psychological aspects, documenting any psychological diagnoses made after the craniopharyngioma diagnosis. Finally, body mass index data at baseline and last follow-up were gathered and reported.

Results

• Patient characteristics

A total of 101 patients between January 1990 and January 2020 were assessed for eligibility. Three patients were excluded from the analysis, one did not meet the inclusion criteria, and the other 2 patients were excluded based on the exclusion criteria. Among the 98 patients in the final analysis, the median age at diagnosis was 20.5 years (1–67), and the median follow-up time was 8.5 years (1.2–32.8). The majority of patients were male (54.1%), histological diagnosis of Adamantinomatous craniopharyngioma (51%), and cystic predominant subtype (59.1%). The median tumor volume was 20.7 cm^3 (0.2–648.9 cm^3). Tumor locations often were adjacent to critical structures, 92.9% attached to the hypothalamic-pituitary region, 86.7% close to cerebral vessels, and 82.7% attached to the optic apparatus. (Table 1)

Concerning the first treatment course, 96 patients (98%) underwent surgical resection. Among them, 13 patients (13.5%) were achieved with GTR and 69 patients (71.9%) were treated with STR. Fourteen patients (14.6%) had no record of surgical extension. Eight patients received post-operative radiotherapy, 1 patient after GTR, and 7 after STR, respectively. Whereas none of the patients were treated with radiotherapy alone, two patients were injected with chemotherapy into the tumor cyst without any tumor resection. (Table 1)

Table 1. Patient Demographics, Tumor and Treatment Characteristics

Characteristics	No. of patients (%)
Total No. of patients	98 (100)
Age, median (range), y	20.5 (1 - 67)
Sex	
Male	53 (54.1)
Female	45 (45.9)
Histology	
Adamantinomatous craniopharyngioma (ACP)	50 (51)
Papillary craniopharyngioma (PCP)	5 (5.1)
Unidentified subtype	43 (43.9)
Predominant characteristic	
Solid predominant	16 (17.2)
Cystic predominant	55 (59.1)
Mixed-solid cystic	22 (23.7)
Tumor volume, median (range), cm^3	20.7 (0.2 – 648.9)
Adjacent site	
Hypothalamus-pituitary axis (HPA)	91 (92.9)
Optic pathway	81 (82.7)
Vessel	85 (86.7)
Surgery	96 (98)
• GTR • STR • No record	13 (13.5) 69 (71.9) 14 (14.6)
Radiotherapy	8 (8.2)
• Adjuvant after GTR • Adjuvant after STR	1 (12.5) 7 (87.5)
Intra-cystic chemotherapy	2 (2)

• Outcomes

After a median follow-up of 8.5 years, sixty-two patients (63.3%) developed disease progression with a median time to progression of 2.4 years. The PFS rates at 5 and 8 years were 39.3% (95% CI: 29.2–49.1%) and 37.9% (95% CI: 27.9–47.8%). (Fig. 1) Only adjuvant radiotherapy positively impacted PFS in univariate and multivariate analyses (HR 0.21, 95% CI: 0.05–0.22, p = 0.03). (Supplement 1) On the other hand, treatment with only chemotherapy injection into the cystic portion of the tumor without tumor removal caused a negative effect on the PFS rate (HR 54.28, 95% CI: 8.9–330.1, p < 0.001). (Supplement 2)

Almost all patients who developed disease progression received salvage treatment, except one who refused further treatment. Currently, she is under continuous clinical observation without any symptoms despite gradual tumor progression. Surgical resection alone was the most common salvage treatment (66.1%), followed by radiotherapy alone (22.6%), then combined STR with postoperative radiotherapy (4.8%) and intra-cystic chemotherapy alone (4.8%). (Supplement 3) The PFS2 rate at 5 years was 45.3% (95% CI: 31.4–58.1%), with the median time to second progression of 3.9 years. (Supplement 4) Not surprisingly, radiotherapy is still the only factor to improve the 5-year PFS2 rate, 78.4% for patients who received radiotherapy compared with 32.4% for patients who did not receive radiotherapy (HR 0.15, 95% CI: 0.02–0.51, p 0.002). (Supplement 5)

Despite a high rate of disease progression, the OS rate still remains high. During the data collection period, only 4 patients died. The OS rate at 5 years and 8 years were 100% and 94.2% (95% CI: 85.2–97.8%), respectively. (Fig. 2) None of the patient factors, tumor factors, or treatment factors showed an impact on OS rates. Even though radiotherapy improved both PFS and PFS2 rates, the benefit did not significantly translate to the OS rate in craniopharyngioma.

Regarding the LC rates, the result showed a similar trend to PFS rates, with 41% at 5 years (95% CI: 30.6–51%) and 39.5% at 8 years (95% CI: 29.2–49.6%). (Fig. 3) Receiving radiotherapy after surgery still has a positive effect on disease control (HR 0.22, 95% CI: 0.05–0.92, p 0.04), and also non-surgical removal treatment with intra-cystic chemotherapy showed a high rate of disease progression (HR 66.8, 95% CI: 9.2–484.1, p < 0.001).

• Radiotherapy failure-free survival (RT-FFS)

Among the patients included in the final analysis, only 38 (38.8%) received radiotherapy in any course of their treatment. While 8 patients received adjuvant radiotherapy after resection in their first course of treatment, 30 patients received radiotherapy with or without combined surgery as their salvage treatment. The median radiation dose administered was 50 Gy, and the most preferred technique was stereotactic radiotherapy (57.9%), followed by intensity-modulated radiotherapy (36.8%). With a median follow-up time of 6.9 years, the RT-FFS rates at 5 and 8 years were both 81.4% (95% CI: 62.9–91.3%). (Fig. 4) The median time to progression was not reached for patients treated with radiotherapy.

• Toxicities

Concerning the endocrine system, this cohort showed that the most common pre-treatment problem on available recorded data was delayed puberty (86%), followed by hypothyroidism (84.7%) and growth hormone deficiency (61.8%). During long-term follow-up, hypothyroidism became the most common adverse event (96%), followed by delayed puberty (77.8%) and lack of growth hormone (17.2%). (Supplement 6) Unfortunately, 40–70% of data were missing in the recorded data in every domain, either at baseline or post-treatment. Among the patients with growth hormone deficiency, 52.4% surprisingly returned to normal during follow-up after the treatment. Not only were hypothyroidism and delayed puberty rarely normalized, but also new late adverse events occurred in 77.8% for hypothyroidism and 25% for delayed puberty. None of the patients with normal growth hormone function developed growth hormone deficiency after treatment.

Furthermore, body mass index (BMI) data were collected from 91 patients from the last follow-up recorded, with 76 patients having pre-treatment BMI data. According to WHO and Asia-Pacific guidelines, the majority of the patients were classified into the obesity group (BMI ≥ 25 kg/m2), 43.4% at baseline and 69.2% at the last follow-up record. While the median BMI at diagnosis was 24.3 kg/m2, the median BMI post-treatment was 26.9 kg/m2. The average BMI change in this cohort indicated an increase of 7 kg/m2 (SD 9.7). Among 76 patients with data available for comparing before and after treatment, around 57.9% remained in the same BMI category. On the other hand, 40.8% of the patients showed an increase in BMI, and most of them turned to the obesity range, while only 1.3% of patients showed a decrease in BMI.

Regarding visual outcomes, this cohort recorded visual acuity both before and after treatment about 52% (n = 51) of all patients. Forty patients (78.3%) were diagnosed with abnormal visual acuity defined as equal to or greater than grade 2 toxicity according to CTCAE version 5 at baseline. Despite great efforts to preserve vision, the abnormal acuity rate was still increased to 86.3% (n = 44) after treatment. The change in visual acuity grading before and after treatment was observed in 49 patients. The majority of them had a stable status (51%), followed by improvements (30.6%), and worsening (18.3%). Furthermore, visual field status was collected from 54 patients (55.1%) prior to the treatment and 72 patients (73.5%) after treatment. Normal visual field was found to be the most common status for both before and after treatment in this report, approximately 44.4% and 43.1% respectively. Then followed by bitemporal hemianopia, about 24.1% at baseline and 22.2% after treatment. In addition, five patients in this cohort were noted to have blindness of both eyes. (Supplement 7) Whereas one patient was defined as blindness from reversible cause and could be resolved with cataract surgery, 4 patients were permanently blind. Three of them developed defects after initial surgery, and the last patient unfortunately developed blindness after the first progression, which could not be reversed after re-operation.

Additionally, post-treatment intracerebral vascular disease was recorded in 6 patients (6.1%). Among them, all patients received surgery. While 2 patients received radiotherapy combined with surgery, 1 patient received intra-cystic treatment combined with surgery, and 3 patients underwent surgery alone. Aside from cerebrovascular disease, a secondary tumor was also a point of interest in our study. There

was only one patient diagnosed with nasopharyngeal cancer, which was discovered 4 years after completing the radiotherapy session. Also, a patient who never received any cranial radiation was noted to have a meningioma in the right frontal lobe. (Supplement 8)

Finally, this cohort reported 6 patients with psychological problems, including mood disorders, emotional control disorders, attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), anxiety, panic, delirium, and insomnia. (Supplement 8)

Discussion

This study reported 30 years of experience in craniopharyngioma treatment in a single university hospital in Thailand. The primary treatment in this cohort exhibited 5-year and 8-year PFS rates of 39.3% and 37.9%, respectively, lower than those reported in several previous studies. [3, 4] The reasons behind this lower PFS rate were the small number of patients who achieved gross total tumor resection (12%) and also the low percentage of patients who underwent adjuvant radiotherapy after partial resection (8%) when compared to other studies. Concerning late radiation toxicities, our institute delayed radiotherapy as much as possible. However, our cohort reported the rate of the PFS2 at 5 years after first salvage treatment at 45.3%, with a median time to second progression of 3.9 years. Our results showed a non-inferior outcome compared to a prior study from Kalapurakal et al., which reported a 5-year second-recurrence-free survival rate of 29%. [12] Jose, et al. also studied the effects of radiotherapy on recurrent craniopharyngioma and showed a 10-year PFS rate of 72%. [13] Despite lower PFS and local control rate shown in this report, the OS rate was still high. With an OS rate at 5 and 8 years of 100% and 94%, our study showed comparable survival to historical studies. [3, 4] The explanation of sustained high OS rates should be due to the effectiveness of salvage treatment, especially radiotherapy. Radiotherapy is very effective not only as an adjuvant for primary treatment, but also for salvage treatment at any time of disease recurrence. Our results showed that adjuvant radiotherapy was the only significant factor in improving PFS and local control on multivariate analysis on the primary treatment course. Furthermore, this study reported the specific outcomes of radiotherapy and showed both 5-year and 8-year RT-FFS rates of 81.4% which are comparable to prior radiotherapy studies. [8–10, 12, 13] Three-year nodular failure-free survival and cystic failure-free survival rates of 95% and 76%, respectively, were reported from Bishop et.al. without any significant difference between IMRT and proton beam therapy technique. [9] Another study from Bischoff, et al. exhibited results of treatment of craniopharyngioma with modern proton beam therapy in Germany, which reported 3-year PFS, and cystic failure-free survival rate of 94.7% and 76.8%, respectively. All local failures in this study were in-field and cystic growth within 12 months after proton therapy were asymptomatic and self-limiting. [8]

Regarding toxicities, endocrinopathy was very common in our cohort and also in prior studies. [6, 14–17] Whereas delayed puberty was most frequently found at diagnosis, about 86%, hypothyroidism was the most common long-term endocrine problem for craniopharyngioma patients, with a cumulative rate of 96%. On the other hand, growth hormone deficiency was reported least at diagnosis (61.8%) and long-term after treatment (17.2%), and approximately 52% of patients with abnormal growth hormone levels

surprisingly returned to normal during long-term follow up after treatment. According to a systematic review from Clark, et al., post-operative endocrine dysfunction was found commonly in pediatric craniopharyngioma patients, approximately 46–59%. [6] While another report about long-term outcomes of adult patients diagnosed with craniopharyngioma from Dogra, et al. showed the same result. Seventy-two percent of 81 patients had ≥ 3 anterior pituitary hormone deficiencies, and 63% of 91 patients had diabetes insipidus. [14] Interestingly, our cohort showed that around 70% of patients had BMIs in the obesity range, and about 30% of patients with available data had an increase in BMI towards the abnormal range during long-term follow up after treatment. Furthermore, we reported an average increase in BMI of 7 kg/m2, which was almost similar to the study from Dogra, et al., which reported a mean difference of BMI of 3.3 kg/m2, and 62% were diagnosed with obesity at the last follow-up. [14] A report from Germany showed 44% of 185 patients developing severe obesity, translating to worse quality of life in almost every domain. [18]

Concerning visual outcomes, decreased visual acuity and visual field defect were still common long-term morbidities even though we tried to preserve as much vision as possible. Unfortunately, visual decline is common and is also related to disease progression and treatment of the suprasellar region with either surgery or radiation. This cohort observed grade 2 or higher adverse events on visual acuity in approximately 80% both before and after treatment. Regarding changes in status between pretreatment and the last follow-up, records were available for only half of all patients. In our study, an improvement in visual acuity was noted in approximately 30% which appears lower than what has been reported in other studies. [6, 16] In addition, normal visual field was found to be the most common status at the beginning and latest follow-up after treatment in this report. In spite of limited data, most findings indicated stability. However, any visual field defect was found in approximately 55% of the cases, which correlates with a previous study. [19] Five patients were defined with blindness of both eyes; one was from a reversible cause and recovered after cataract surgery, three were permanently blind from the initial surgery, and the last one developed persistent visual loss after the first tumor progression.

Other toxicities were rare but still found in this study, with around 6% intracerebral vascular defects, 6% psychological problems, and 2% secondary tumors. Results from our research correlate with results from previous studies. [17, 20–22]

Despite some limitations in this study due to retrospective data collection, e.g. advances in treatment during these three decades and missing data, especially for toxicities, this cohort has some strengths. First, this is a 30-year cohort from a single university-based hospital with almost a hundred patients, which can provide a long course of natural history in this rare disease and long-term treatment outcomes. Finally, we also reported failure rates focusing on radiotherapy treatment, which can provide interesting results of how effective radiotherapy treatment on craniopharyngioma can be, regardless of the timing of treatment.

Conclusion

Craniopharyngioma is a rare brain tumor that has a favorable prognosis for overall survival, even if it tends to progress locally after inadequate surgical treatment. Radiotherapy is an effective treatment in both post-operative situation after suboptimal surgical resection and salvage treatment after progressive disease. Conversely, intra-cystic chemotherapy treatment without surgery showed detrimental outcomes. Late toxicities are still challenging for the treatment, especially endocrinopathy and visual defects, and multidisciplinary team discussion should be considered.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Thawanrat Pandaeng, Rasin Worawongsakul, and Padcha Tunlayadechanont. The first draft of the manuscript was written by Thawanrat Pandaeng, and Rasin Worawongsakul, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

All data generated and analyzed during this study are included in this published article and its supplementary information files. However, the datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The protocol of study was reviewed and approved by the institutional ethics committee (MURA2023/340).

Consent to participate

Informed consent was obtained from all individual adult participants or from the parents in minor participants before the treatment. The requirement for re-collecting the informed consent was waived by

the IRB due to retrospective study.

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Figures

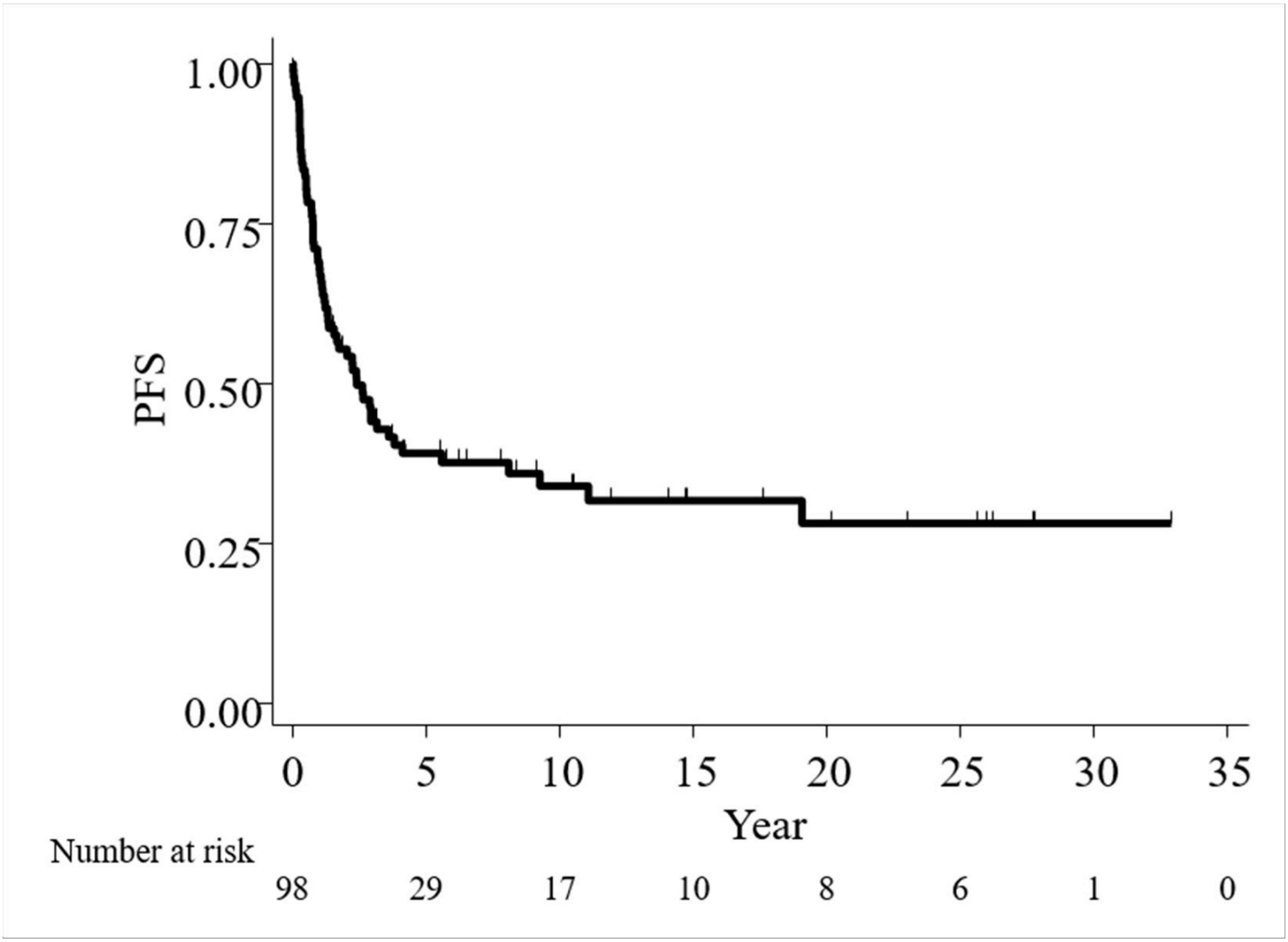


Figure 1

Kaplan–Meier estimates the progression-free survival rate for all patients in this study

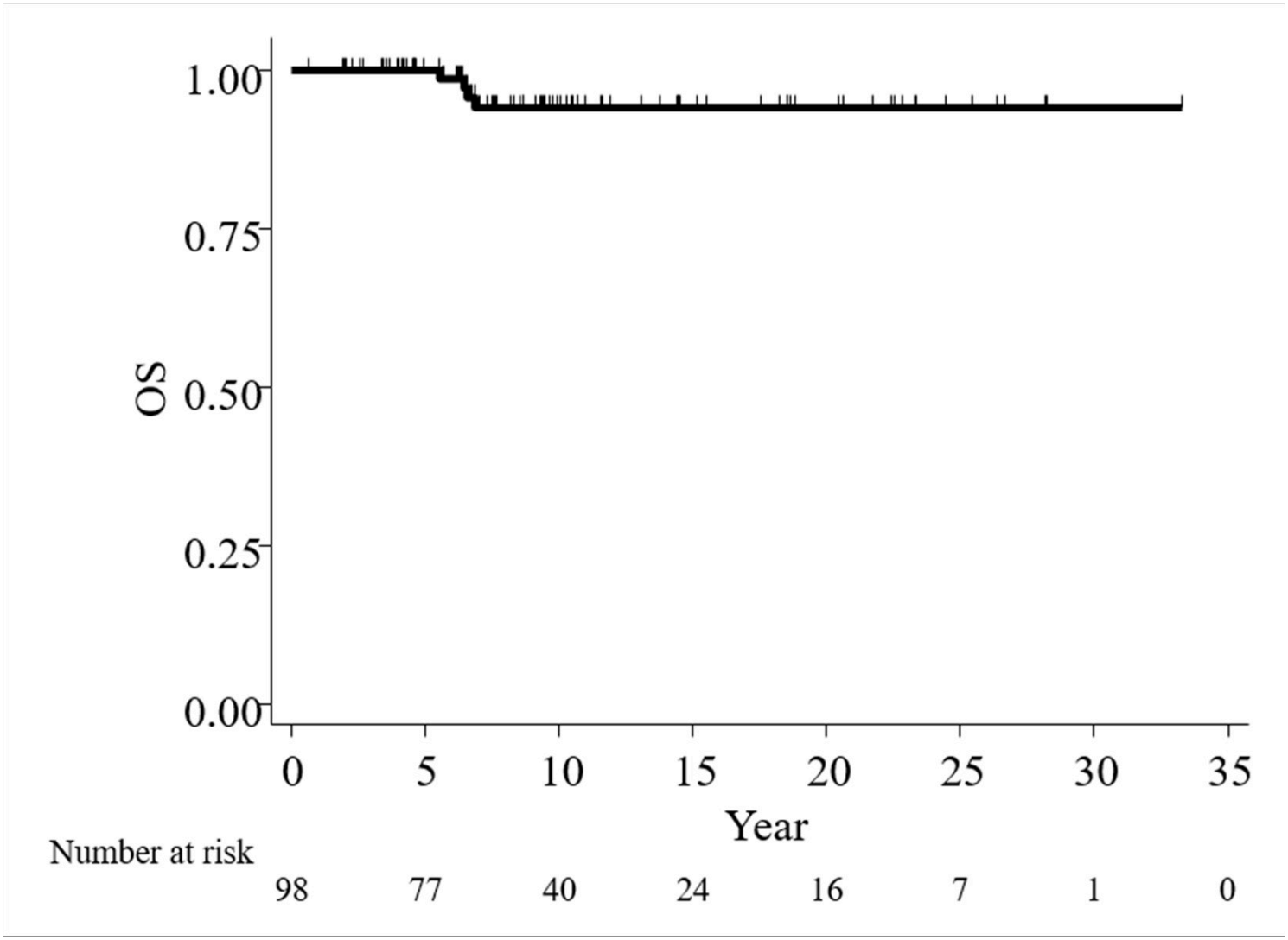


Figure 2

Kaplan–Meier estimates the overall survival rate for all patients in this study

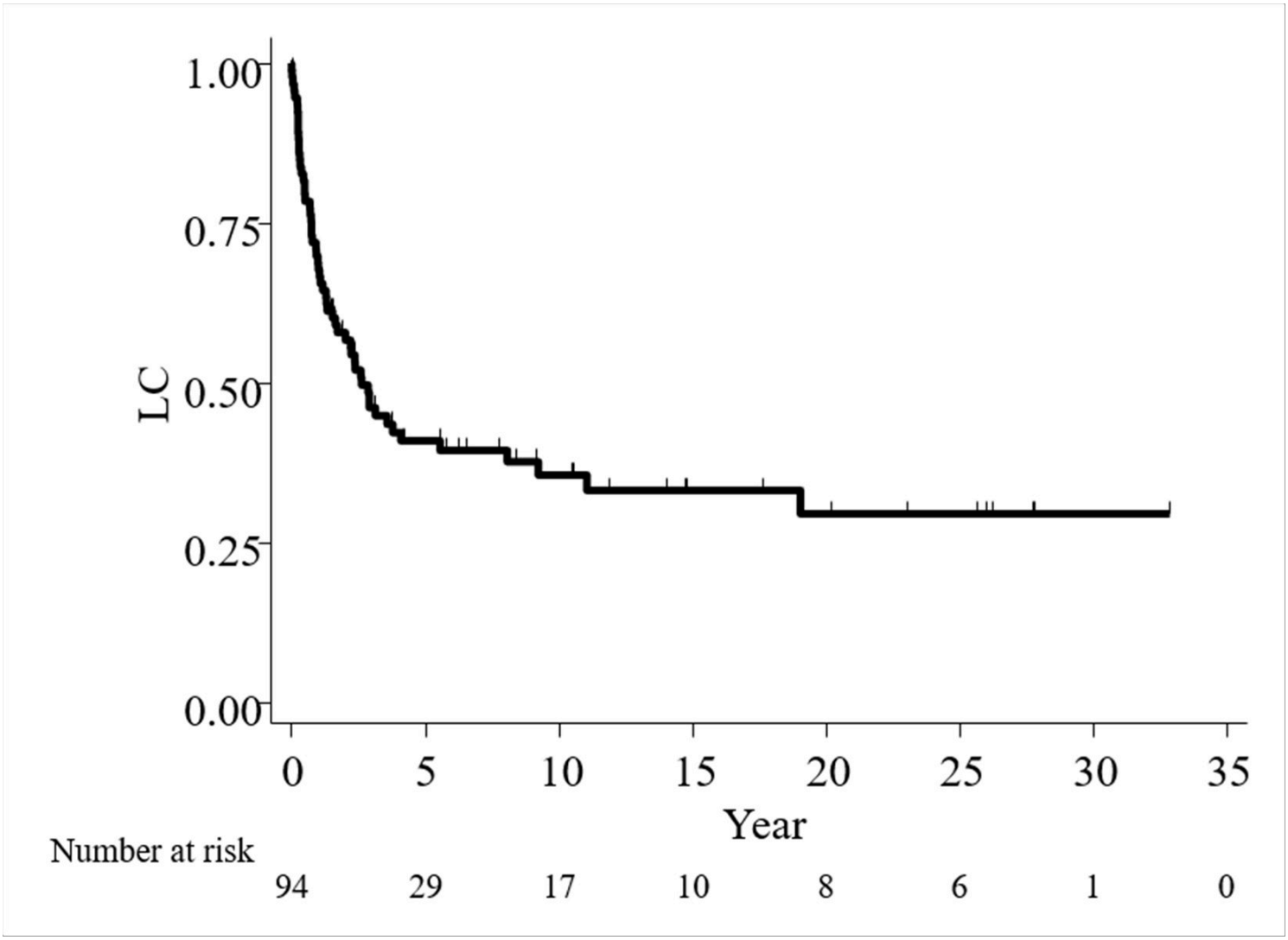


Figure 3

Kaplan–Meier estimates the local control rate for all patients in this study

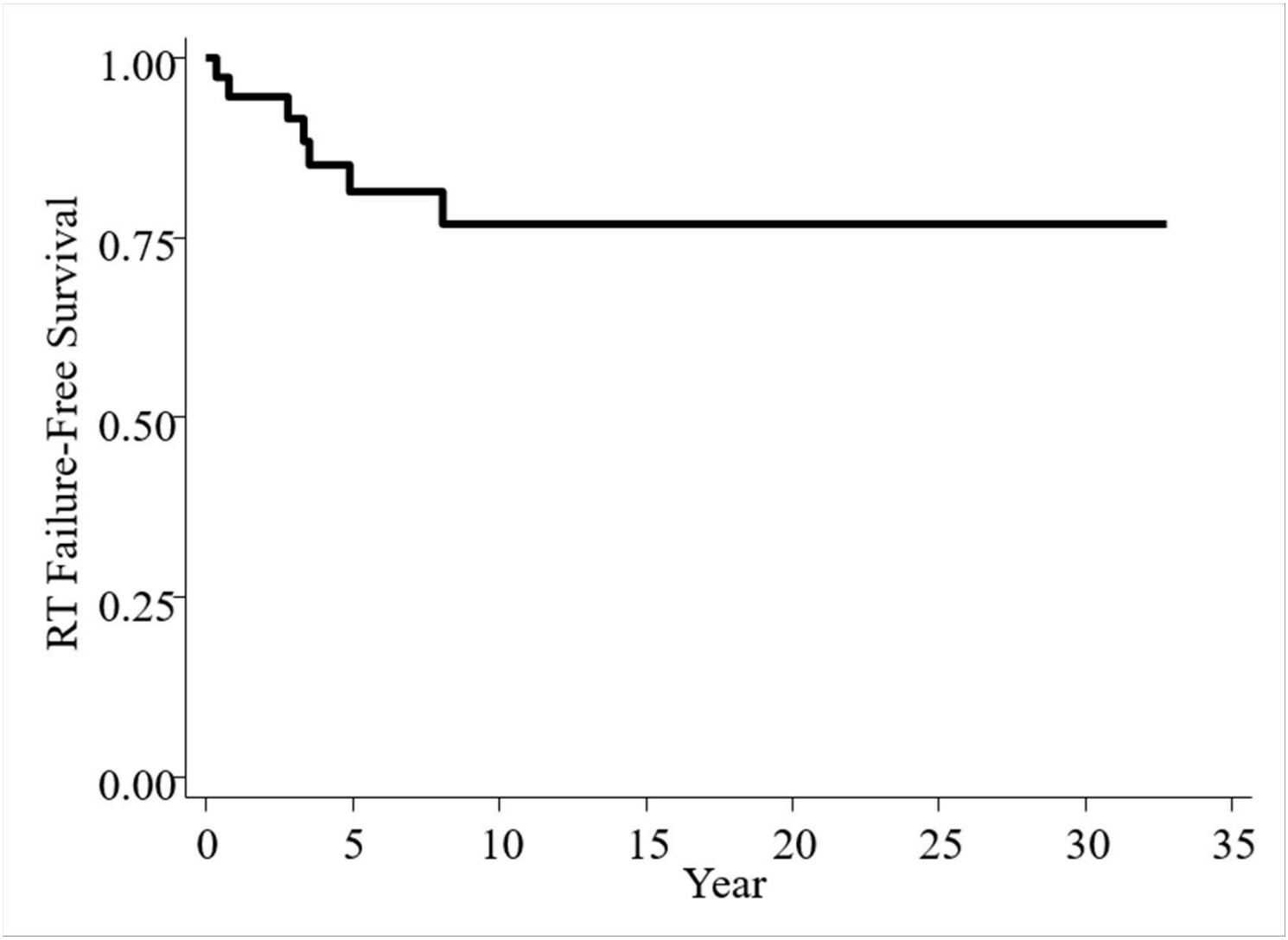


Figure 4

Kaplan–Meier estimates the radiotherapy failure-free survival rate for all patients who received radiotherapy in any course of treatment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarydata.docx